Cardiovascular Risk Reduction and Other Co-Morbidities in Type 2 Diabetes

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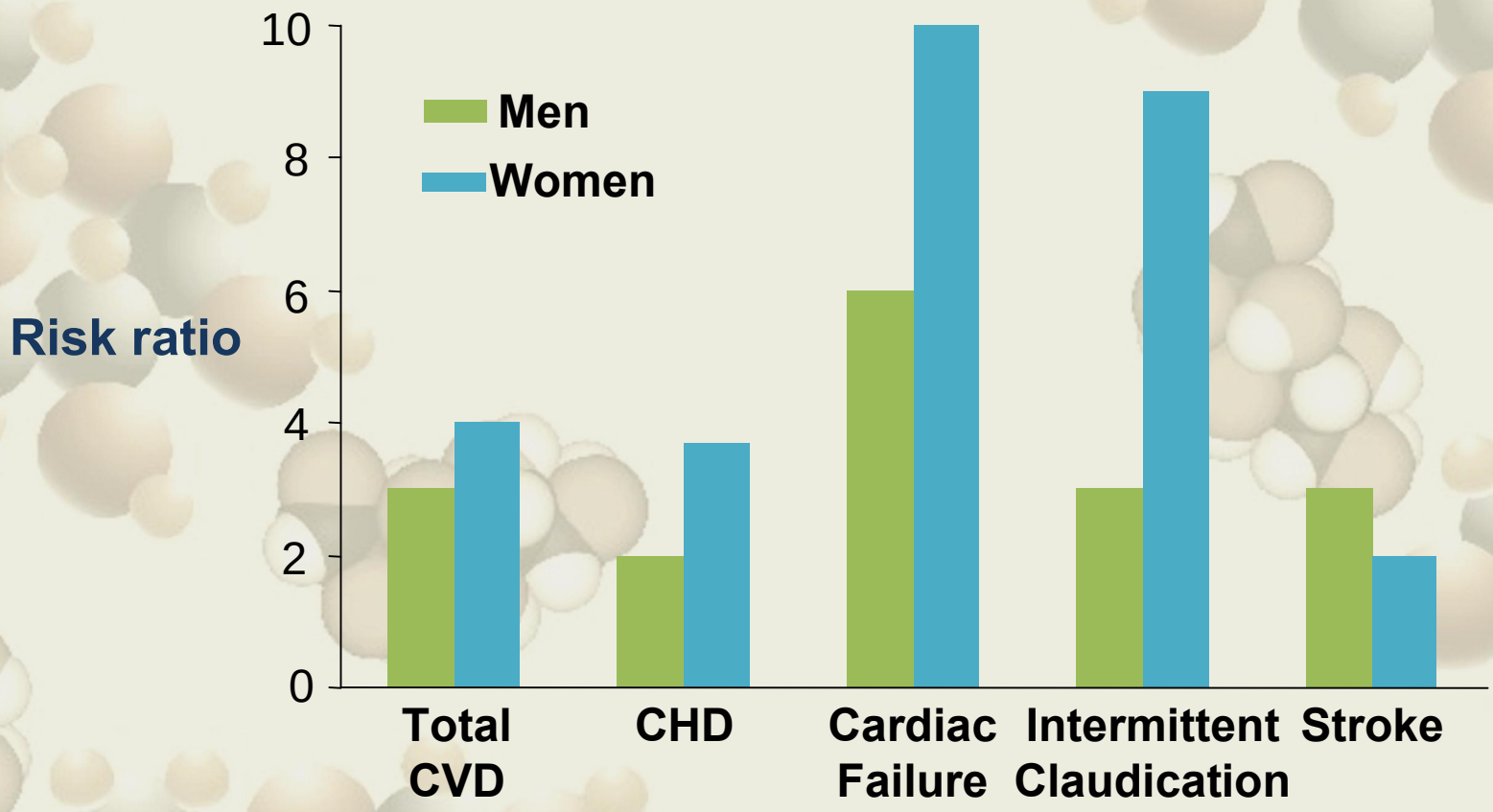
Cardiovascular Risk Reduction and Other Co-Morbidities in Type 2 Diabetes

- Describe the relationship between major CV risk factors and CVD outcomes
- Identify therapeutic modalities available to practitioners to improve CV risk factors
- Understand the implications of recent large trials on clinical decisions guiding choice and targets for blood pressure and lipid abnormalities
- Discuss other co-morbid/microvascular conditions associated with type 2 diabetes

Diabetes is a Vascular Disease



Wilson PWF, et al. eds. *Hyperglycemia, Diabetes, and Vascular Disease. New York: Oxford University Press*; 1992:21-29.

Established Modifiable Cardiovascular Risk Factors in Type 2 Diabetes

UKPDS 23

Position in Model	Variable	P Value*
First	Low-density lipoprotein cholesterol	<.0001
Second	High-density lipoprotein cholesterol	.0001
Third	Hemoglobin A1C	.0022
Fourth	Systolic blood pressure	.0065
Fifth	Smoking	.056

Adjusted for age and sex in 2693 white patients with type 2 diabetes with dependent variable as time to first event.
*Significant for CAD (n=280). P values are significance of risk factors after controlling for all other risk factors in model.

Turner RC et al. *BMJ*. 1998;316:823-828.

Known Risk Factors for CVD

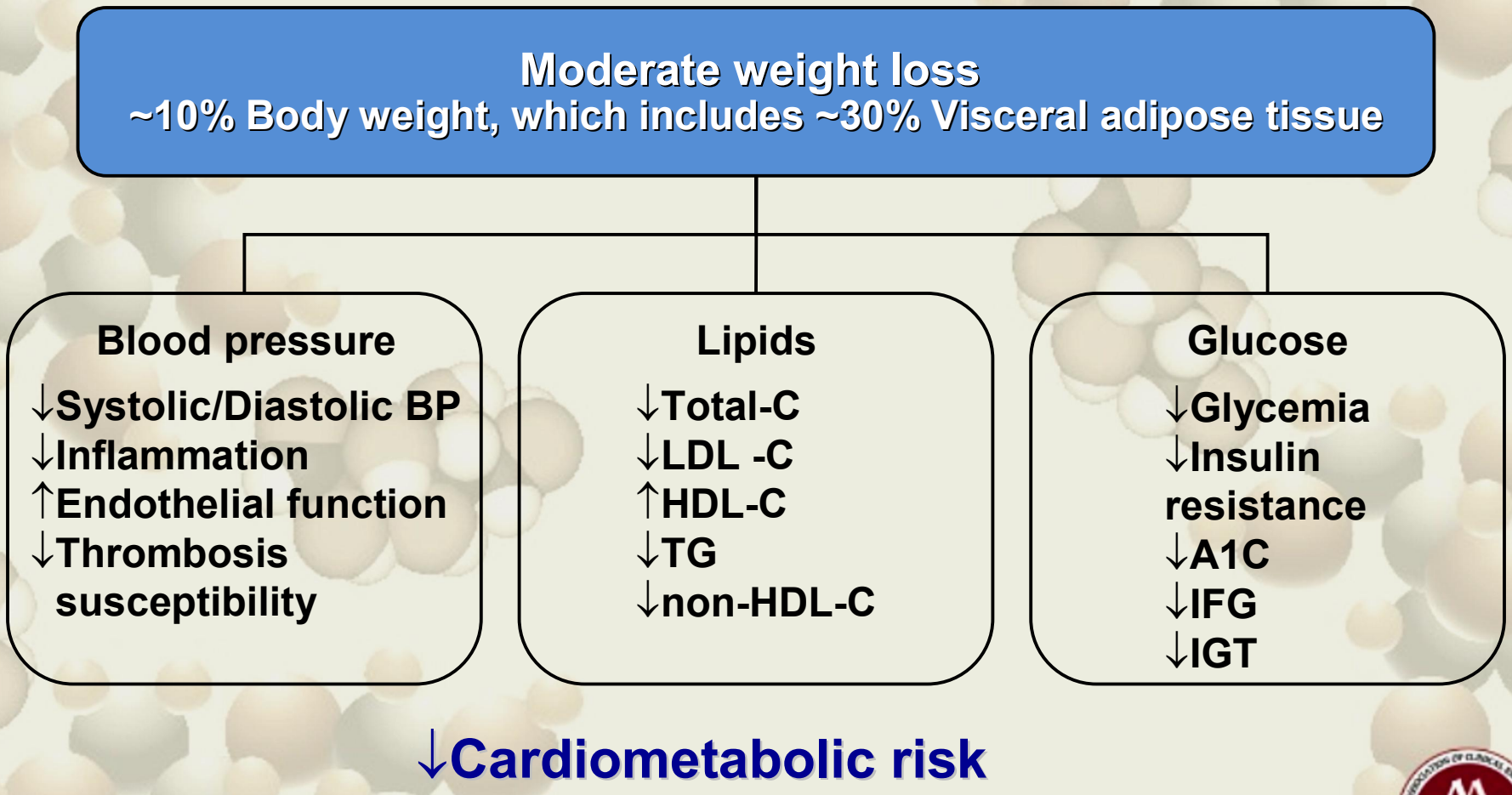
Major Risk Factors	*Additional Risk Factors*	*Non-Traditional Risk Factors*
Advancing age[a,d]	Obesity, abdominal obesity[c,d]	Elevated Lp(a)
High total serum cholesterol level[a,b,d]	Family history of hyperlipidemia[d]	Elevated clotting factors
High Non-HDL[d] [?]	Small, dense LDL-C[d]	Inflammation markers (hsCRP; Lp-PLA_2)
High low-density lipoprotein cholesterol (LDL-C)[a,d]	⇑ Apo-B[d]	Hyperhomocysteinemia
Low high-density lipoprotein cholesterol (HDL-C)[a,d,e]	⇑ LDL particle number	Apolipoprotein E (apoE) 4 isoform
Diabetes mellitus[a,b,c,d]	Fasting/postprandial hypertriglyceridemia[d]	Elevated uric acid
Hypertension[a,b,c,d]	Polycystic Ovary Syndrome (PCOS)[d]	
Cigarette smoking[a,b,c,d]	Dyslipidemic triad[f]	
Family history of CAD[a,d,g]		

[a] Risk factors identified in the Framingham Heart study
[b] Risk factors identified in the MRFIT study
[c] Risk factors identified in the INTERHEART study
[d] Risk factors identified in guidelines/position statements (NCEP ATP III, AACE PCOS Position Statement, AACE IRS Position Statement, ADA Standards of Care 2009, ADA/ACC Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk)
[e] High HDL-C is a negative risk factor

National Cholesterol Education Program, Adult Treatment Panel III: Final Report. NIH Publication No. 02-5215. September 2002; AACE. *Endocr Pract*. 2005;11(2):126-134; ACE. *Endocr Pract*. 2003;9(3):240-252. Yusuf S et al. *Lancet*. 2004;364:937-952; ADA. *Diab Care*. 2011;34(S1):S11-S61; Chobanian A et al. *JAMA*. 2003;289:2560-2572; Kastelein JJP, et al. *Circulation*. 2008;117:3002-3009; Brunzell JD et al. *Diab Care*. 2008;31(4):811-822.

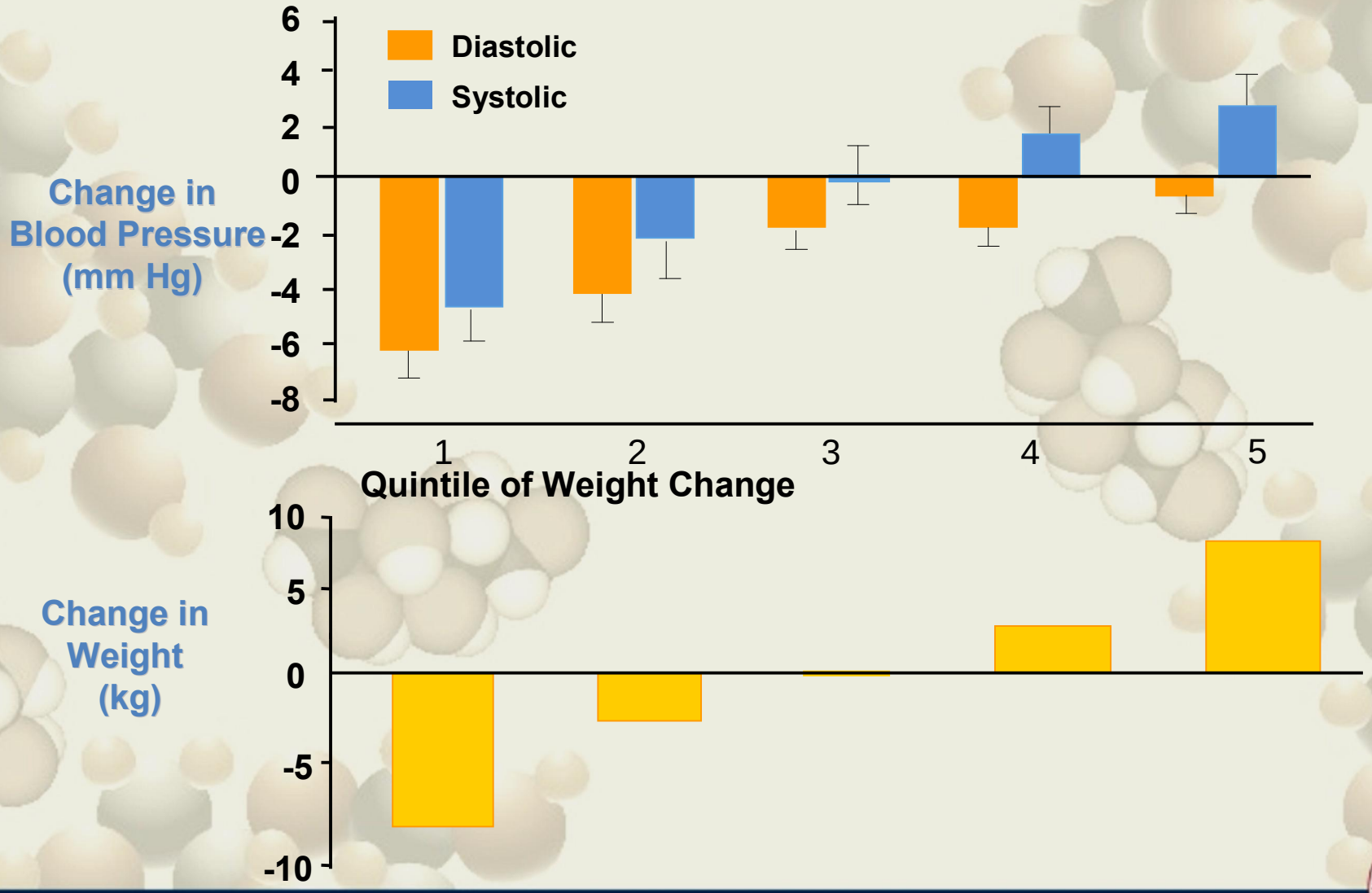
ADIPOSITY

Even Moderate Weight Loss May Improve Cardiometabolic Risk



Manson JE et al. *Arch Intern Med*. 2004;164:249-58. Després J-P et al. *BMJ*. 2001;322:716-20.

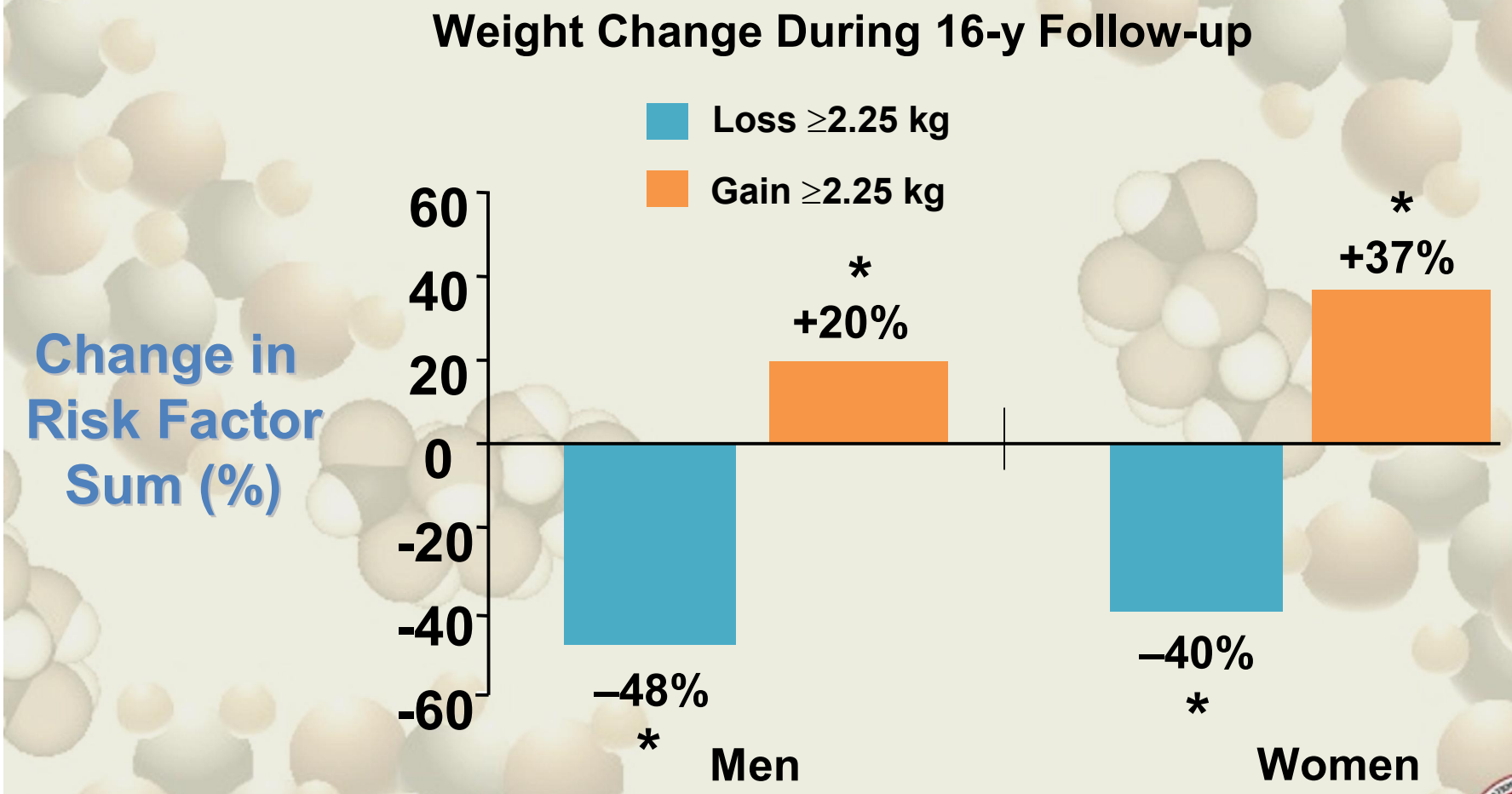
Relationship Between Changes in Weight and Blood Pressure: Trials of Hypertension Prevention II



Stevens, et al. *Ann Intern Med.* 2001;134:1.

Relationship Between Weight Change and CHD Risk Factor Sum: Framingham Offspring Study

Low HDL-C, high cholesterol, high BMI, high systolic BP, high triglyceride, high glucose

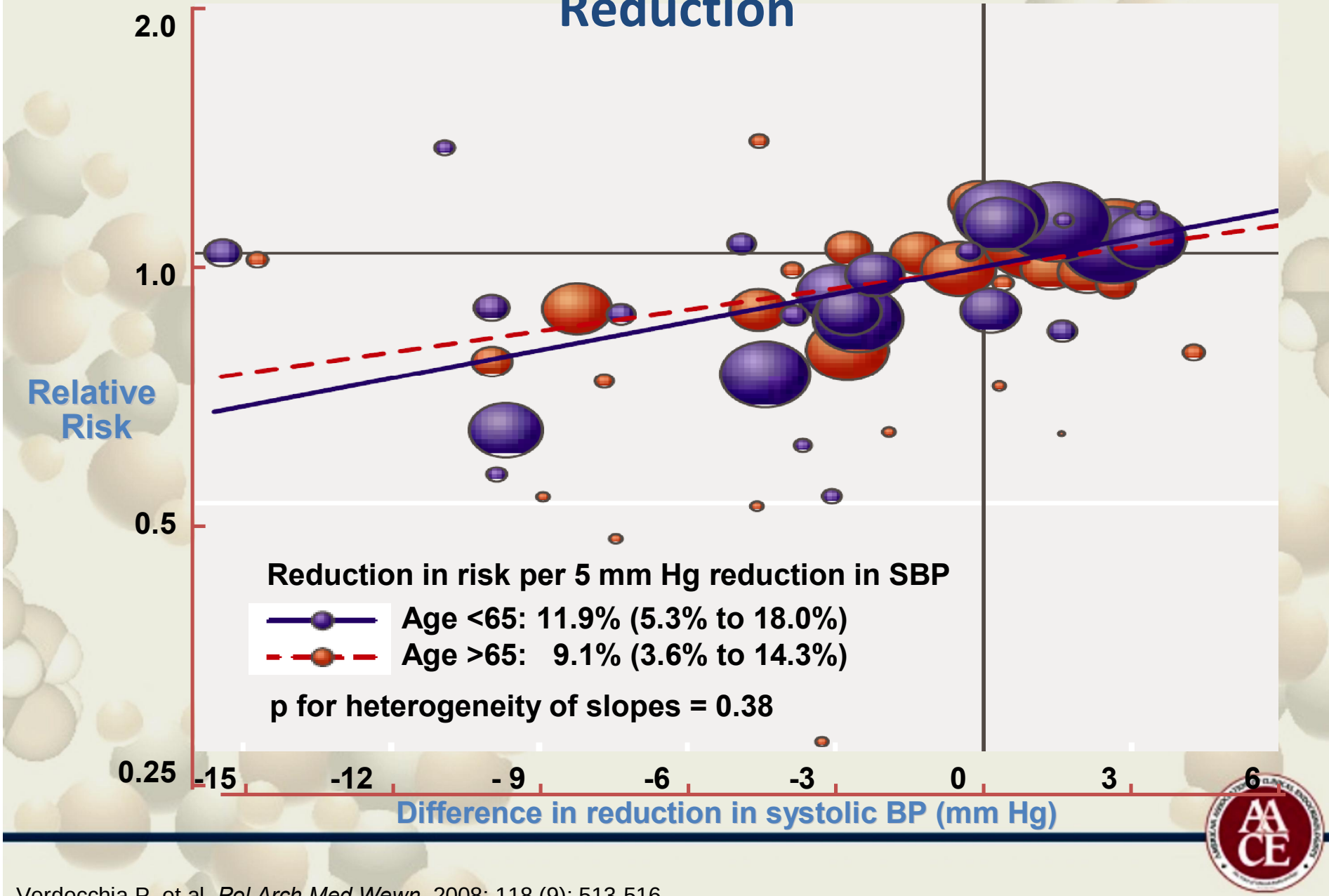


*P <0.002 vs baseline.

Wilson, et al. *Arch Intern Med.* 1999;159:1104.

Hypertension

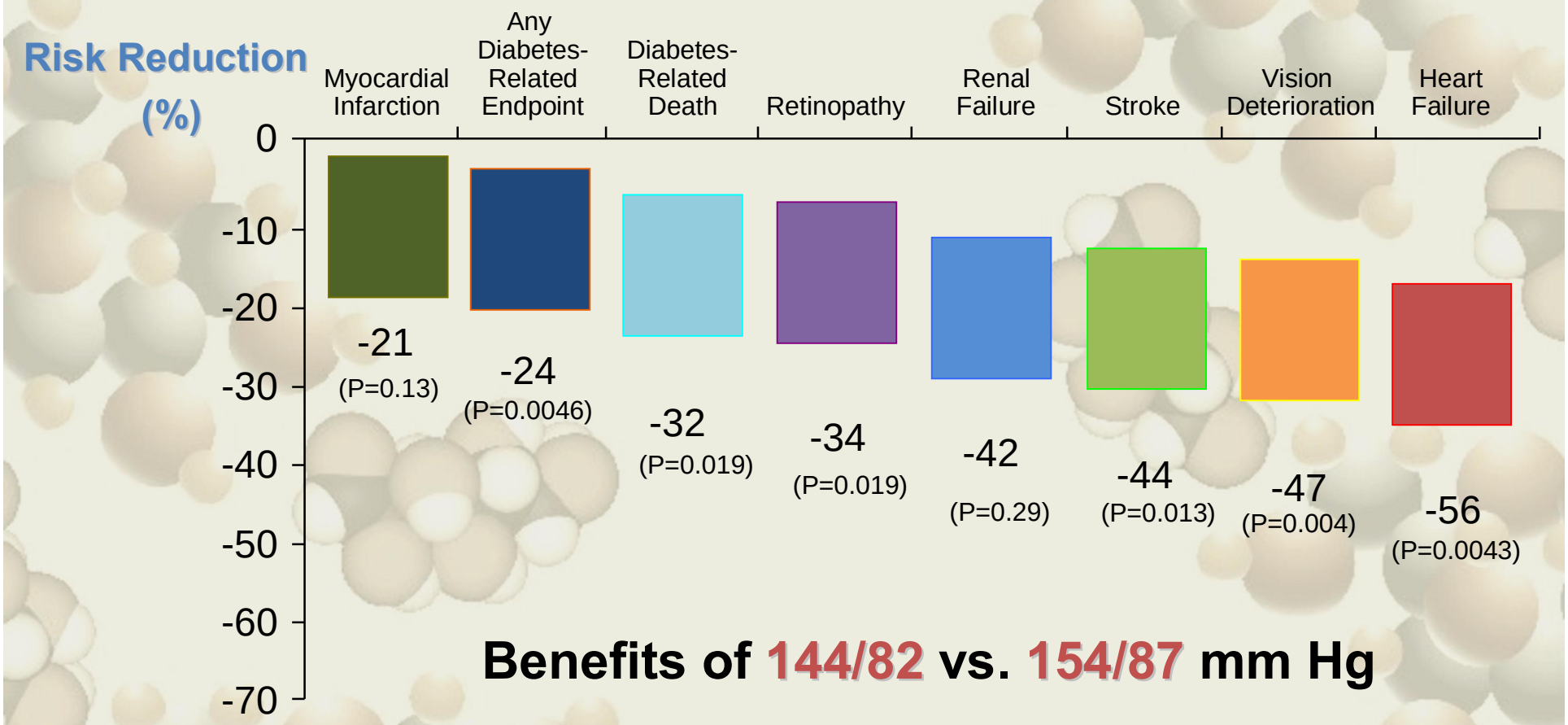
Meta-Regression Analysis of Major CV Events and BP Reduction



Verdecchia P. et al. *Pol Arch Med Wewn*, 2008; 118 (9): 513-516

UKPDS: Blood Pressure Control in Type 2 Diabetes

Effect of BP Lowering on Risk of Micro- and Macrovascular Complications

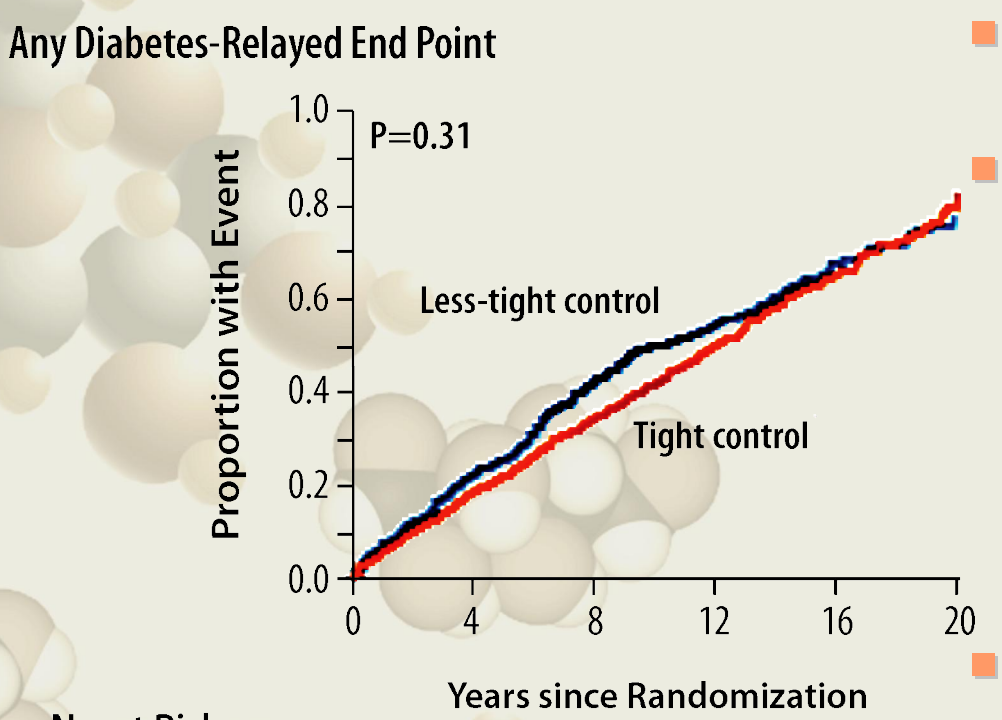


Benefits of 144/82 vs. 154/87 mm Hg

UKPDS Group. *UKPDS 38. BMJ.* 1998;317:703-713.

UKPDS: Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes

Good BP control must be continued if benefits are to be maintained

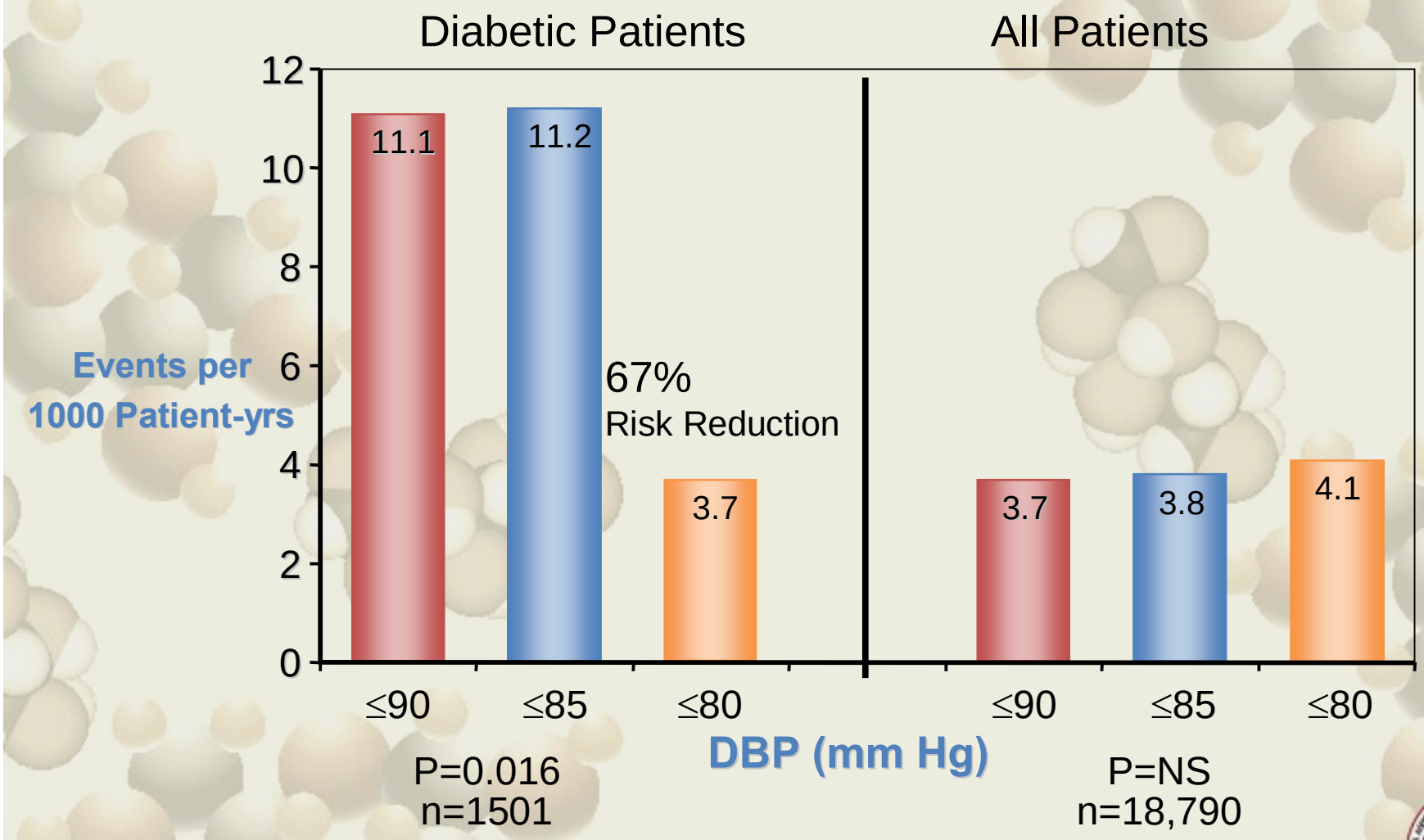


No. at Risk						
Less-tight control	390	296	214	138	68	11
Tight control	758	601	458	296	133	19

- Differences in BP disappeared within 2 years of trial termination
- Post-trial follow-up revealed that the significant relative risk reduction achieved with tight BP control during the trial were not sustained for:
  - Any diabetes-related end point,
  - Diabetes-related death,
  - Microvascular disease, or
  - Stroke
- A risk reduction for peripheral vascular disease associated with tight BP control became significant (P = 0.02) during the follow-up

Holman et al. *N Engl J Med*. 2008. 359;15

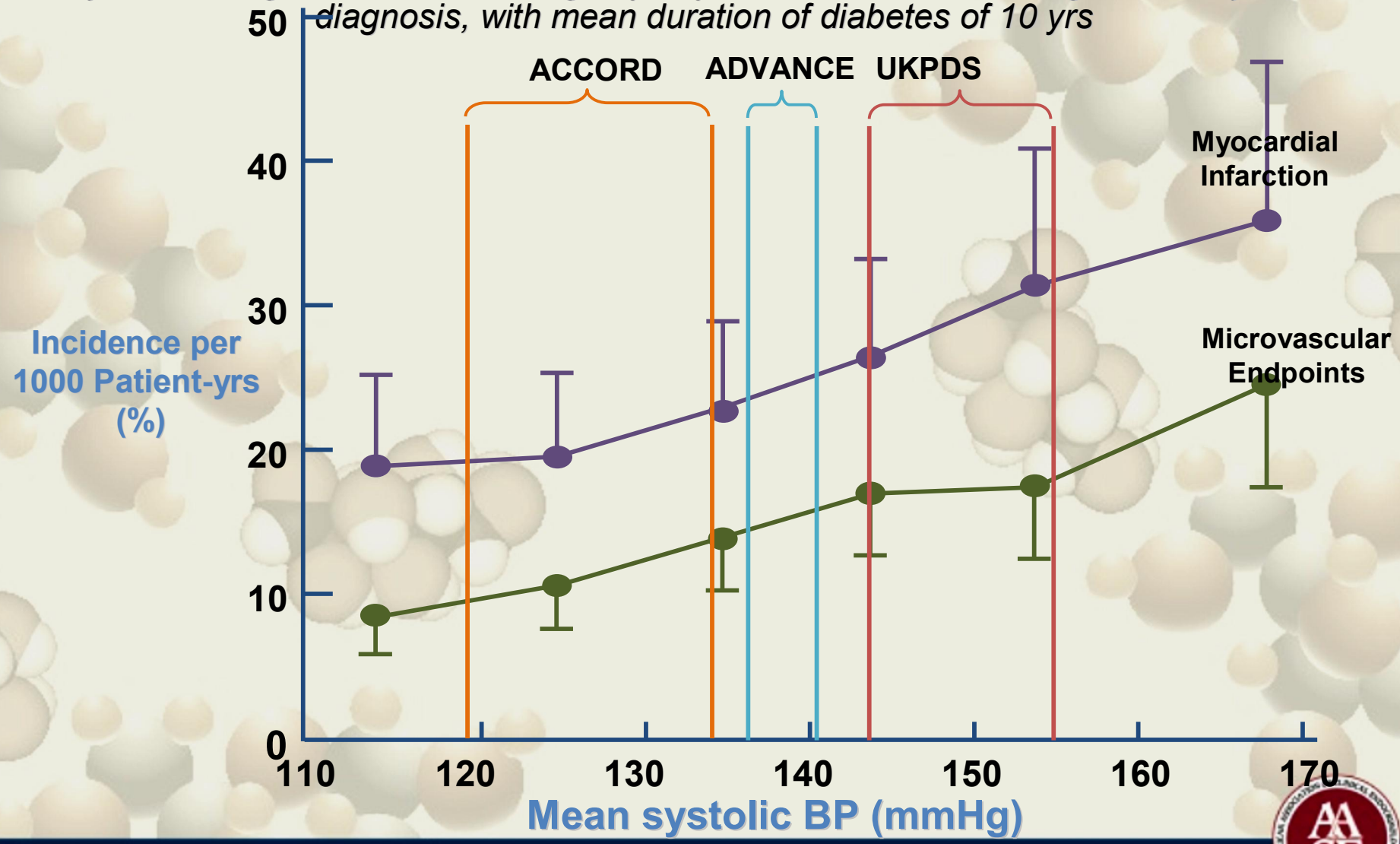
HOT Trial: Effect On CV Mortality – 4 Years



Hansson L et al. *Lancet.* 1998;351:1755

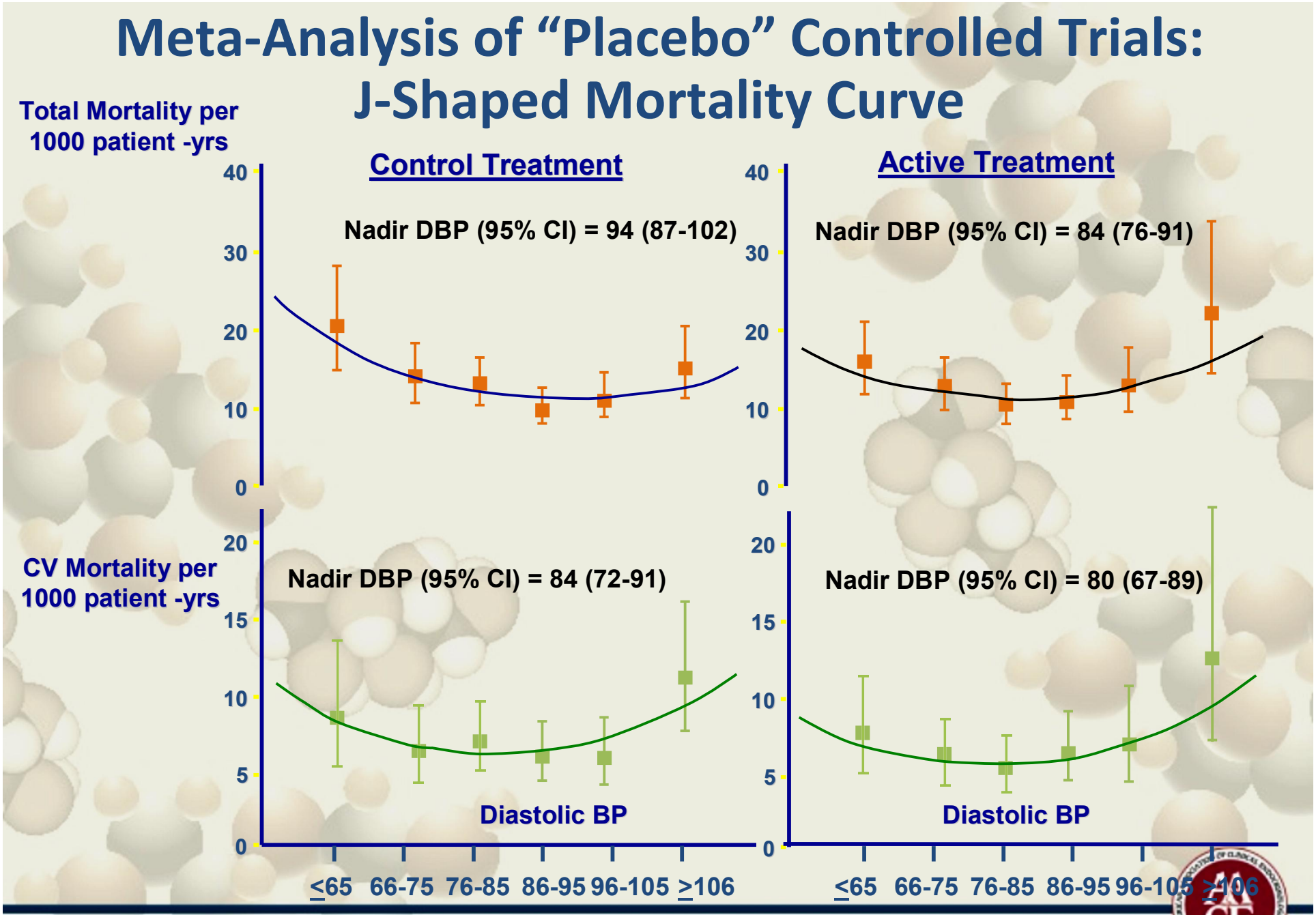
ADVANCE & ACCORD In Context – UKPDS

Incidence of myocardial infarction and microvascular end points by mean systolic BP, adjusted for age, sex, and ethnic group expressed for white men aged 50-54 years at diagnosis, with mean duration of diabetes of 10 yrs



Alder AI et al. *BMJ*. 2000 Aug 12;321(7258):412-9.

Meta-Analysis of "Placebo" Controlled Trials: J-Shaped Mortality Curve



Boutitie et al. *Ann Intern Med*. 2002 Mar 19;136(6):438-48.

Conclusion

- Retrospective analyses do not provide consistent evidence regarding a treatment induced ñJ-shaped curveòin ñhigh riskòpatients
- Post-hoc analyses of trials do not provide consistent estimates of the nadir of blood pressure values and the increased incidence of CV outcome events associated with the ñJ-shaped curveòphenomenon
- Outcome trials suggest that while there is a need to exercise some caution and to accommodate the needs of individual patients, the focus on achieving good systolic BP control to current targets should not be lost

ESH–ESC and JNC 7 Guidelines Recommend Target BP Goals for Uncomplicated and Complicated Hypertension

Type of hypertension	BP goal (mmHg)
Uncomplicated	<140/90
Complicated	
Diabetes mellitus	<130/80
Kidney disease	<130/80*
Other high risk (stroke, MI)	<130/80

Lower if proteinuria is >1 g/day

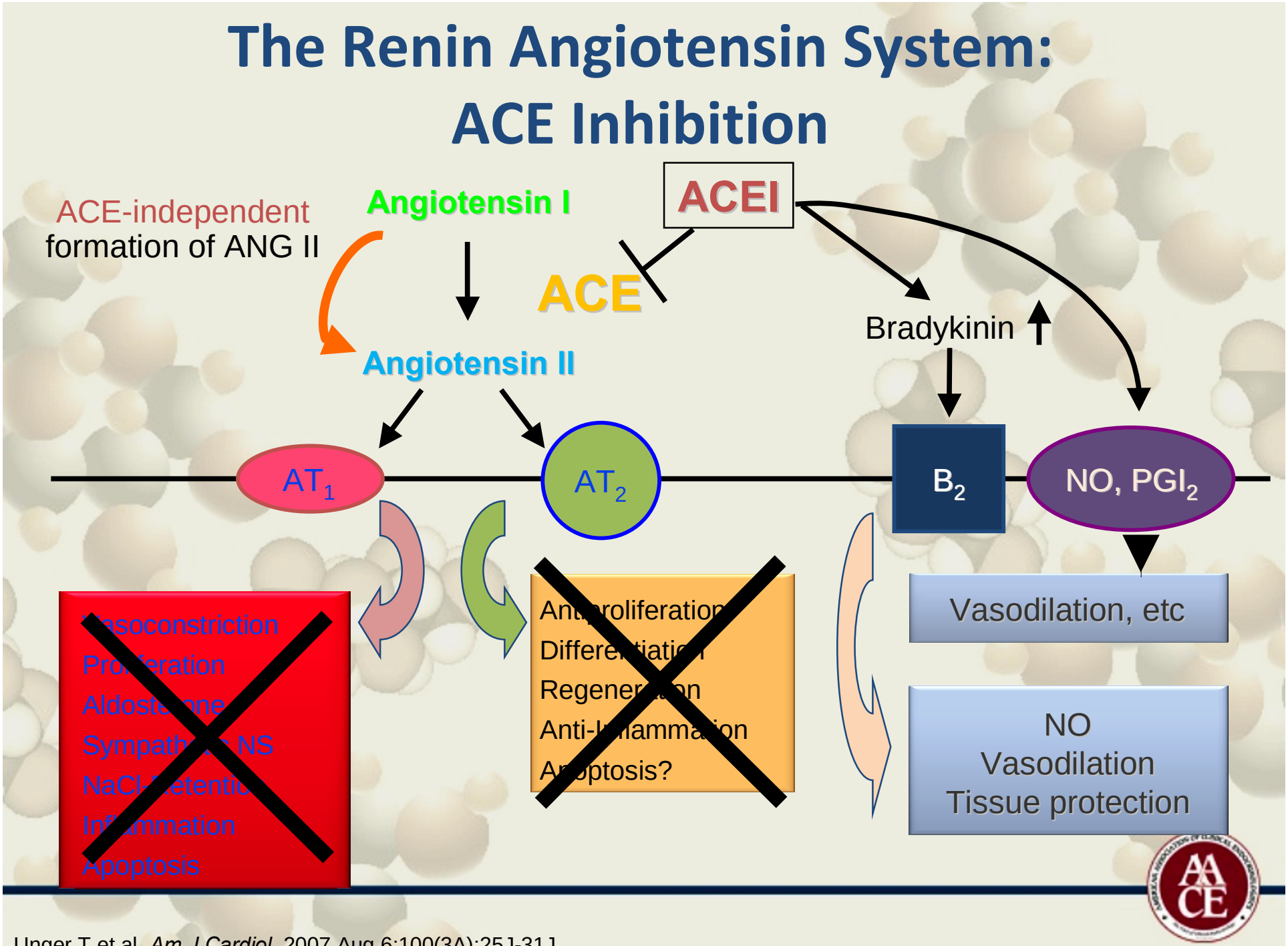
Task Force of ESHï ESC. *J Hypertens* 2007;25:1105; Chobanian et al. *Hypertension.* 2003;42:1206ï 52

Antihypertensive Therapy and Type 2 Diabetes

- Optimal blood pressure (BP) control with different classes of antihypertensives has shown important benefits in reducing the risks of macrovascular and microvascular disease
- It has been suggested that antihypertensives that block the renin-angiotensin-aldosterone system (RAAS) might offer additional benefit beyond BP control by way of delaying the progression of diabetic nephropathy
- While angiotensin-converting enzyme (ACE) Inhibitors have proven benefit in diminishing the progression of nephropathy in type 1 diabetes, equivalent data in type 2 diabetes is limited

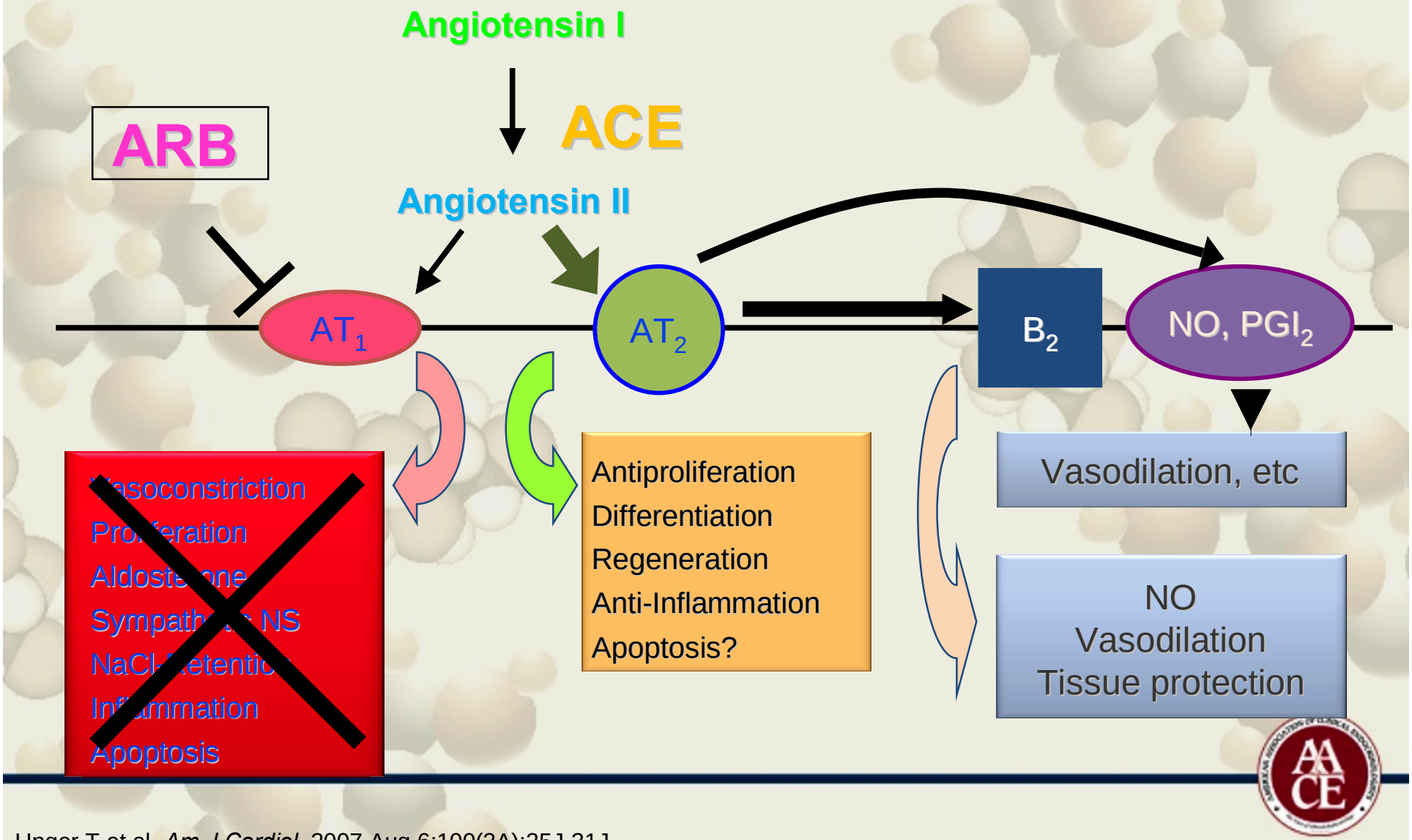
Eberhard R,et al *Cardiovasc Diabetol*. 2010; 9: 60. Grossman E, et al. *Am J Hypertens.* April 28, 2011 Apr 28;1-13.

The Renin Angiotensin System: ACE Inhibition



Unger T et al. *Am J Cardiol*. 2007 Aug 6;100(3A):25J-31J.

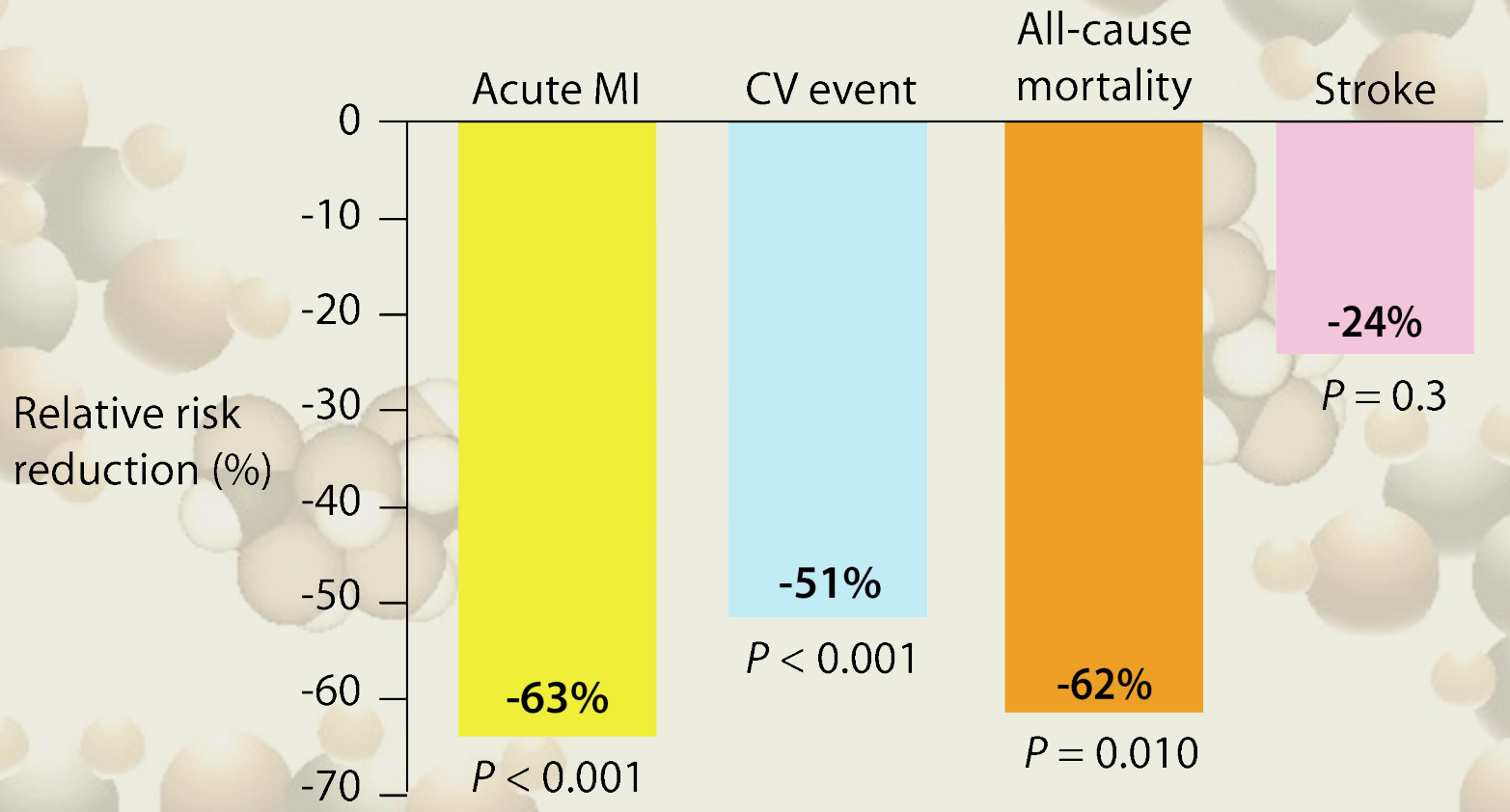
The Renin Angiotensin System: AT_1 Blockade



Unger T et al. *Am J Cardiol.* 2007 Aug 6;100(3A):25J-31J.

CV Risk Reduction with ACEIs in Type 2Diabetes: ABCD, CAPPP, and FACET

ACEI (n = 733) vs other antihypertensive agents (n = 689)



Pahor M. et al. *Diabetes Care.* 2000;23:888-892.

ACEI/ARB in TYPE 2 DM

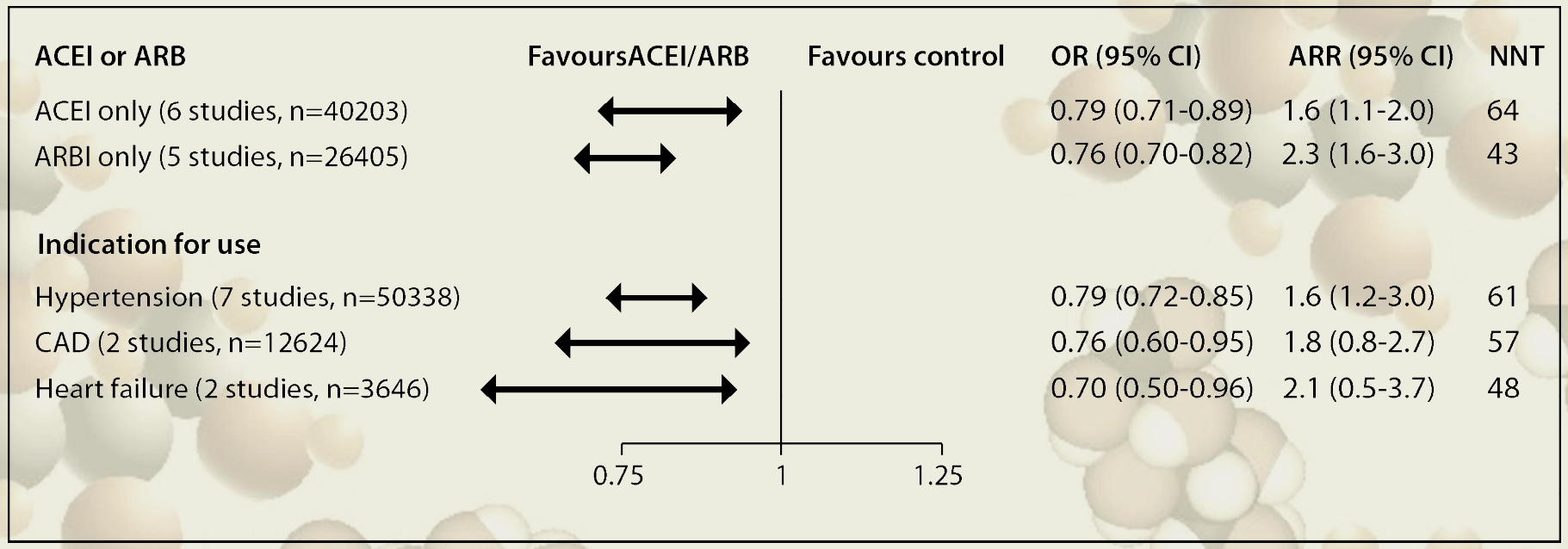
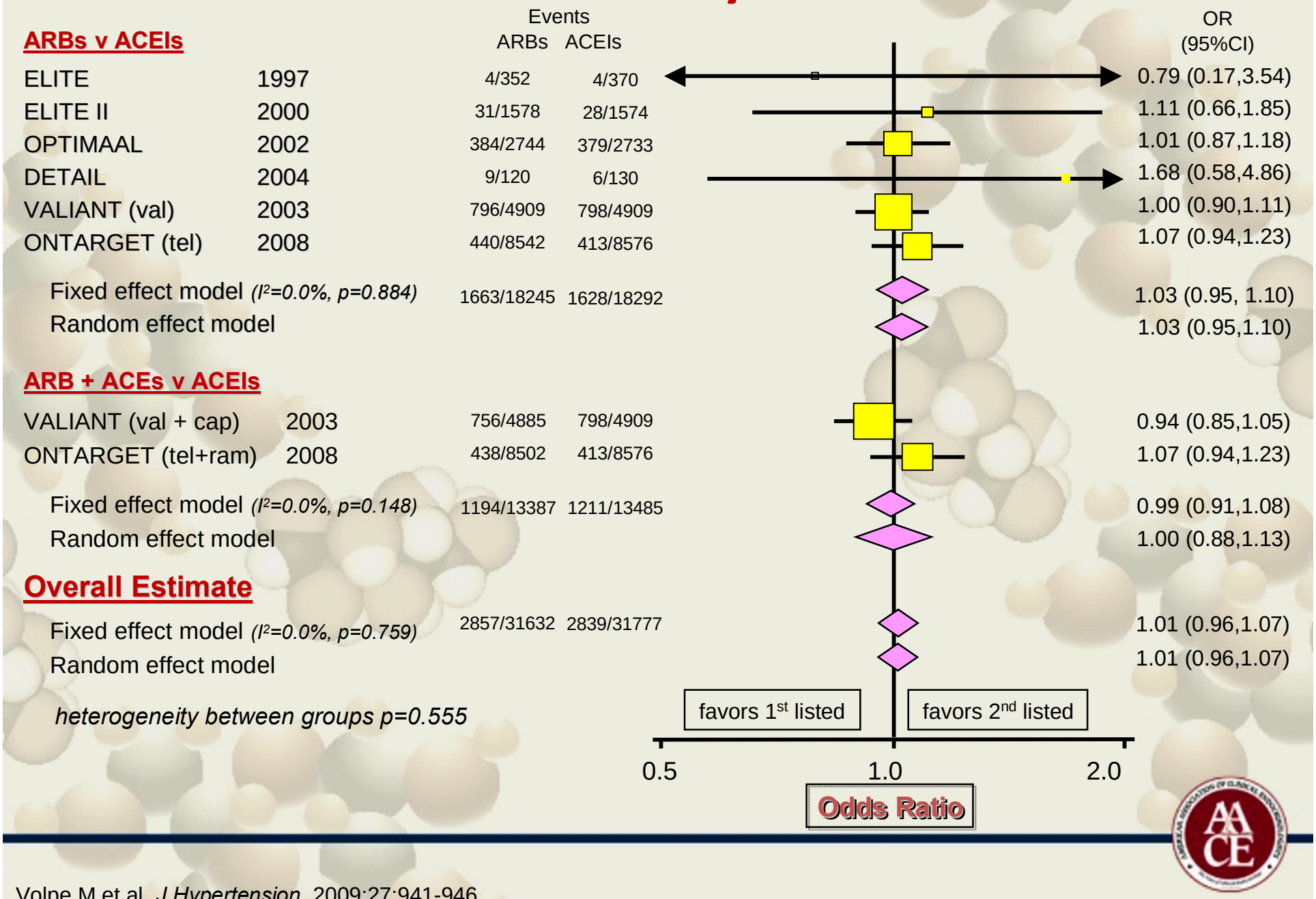


Figure 6: **Risk of developing type 2 diabetes with ACE inhibitors or ARBs compared with other antihypertensive treatment**

In this meta-analysis, ACE inhibitors lower the risk of developing type 2 diabetes by 21% and ARBs by 24%. The effect is independent from the indication for the use of the ACE inhibitor or ARB. In another meta=analysis, ACE inhibitors and ARBs reduced the risk of onset of type 2 diabetes by 27% and by 23%, respectively. Reproduced from *The American Diabetes Association*. Gillespie et al. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; 28:2261-66. © 2005 The American Diabetes Association. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker ARR=adjusted relative risk. CAD=coronary artery disease. NNT=number needed to treat. OR=odds ratio.

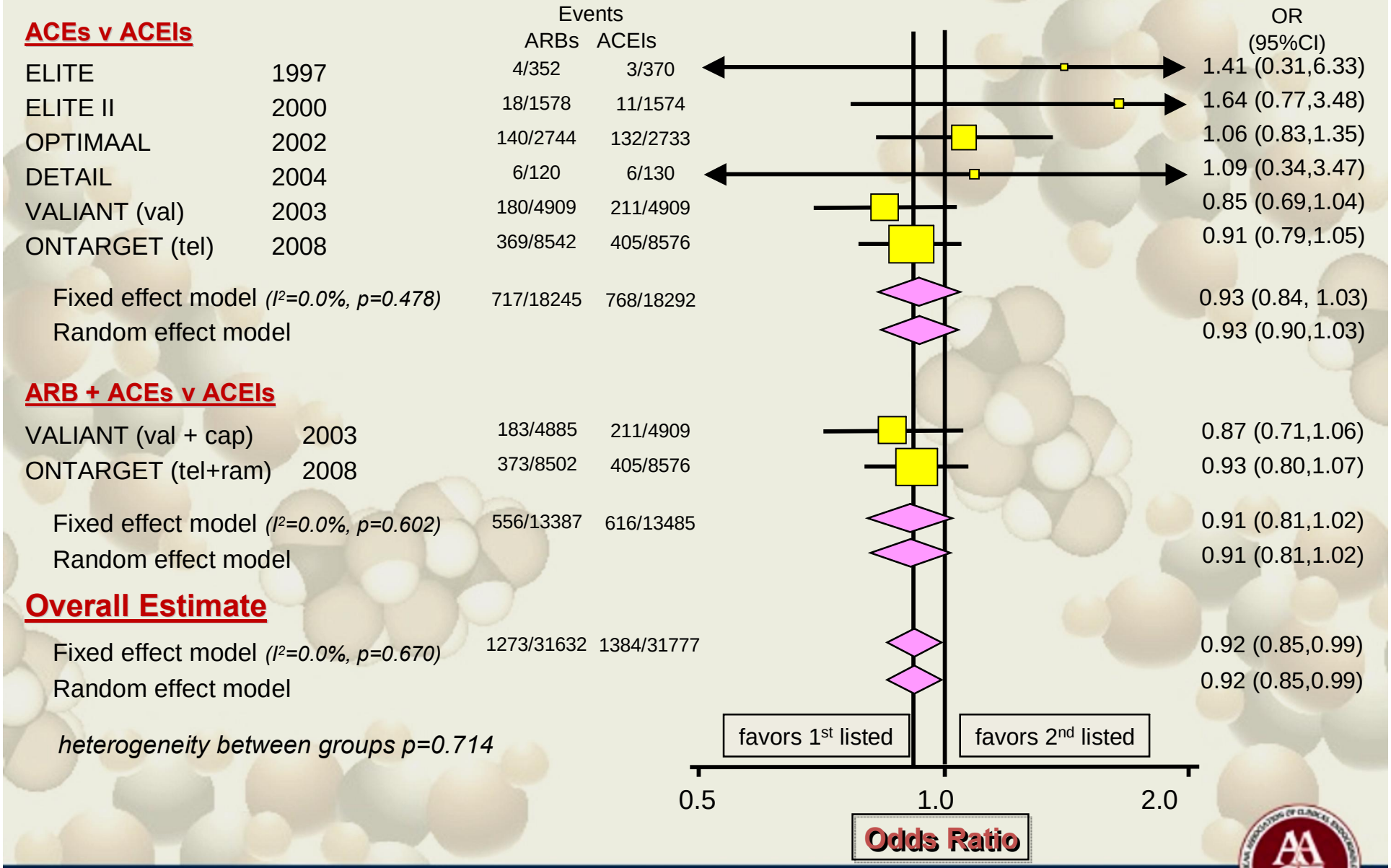
Schmieder RE et al. *The Lancet*. 7 April 2007. 369(9568)1208ï 1219.

ACEIs vs ARBs: Risk of Myocardial Infarction



Volpe M et al. *J Hypertension*. 2009;27:941-946.

ACEIs vs ARBs: Risk of Stroke



Angeli F. et al. *Expert Rev Cardiovasc Ther.* 2008 Oct;6(9):1171-4.

β-Blockers in Diabetes: GEMINI

- Study Design
  - Carvedilol vs metoprolol
  - 1235 diabetic patients with hypertension and receiving RAS blockers
  - 35-week follow up
- Results*
  - Similar decreases in BP
  - Carvedilol had no effect on A1C; metoprolol ↑ A1C
  - Carvedilol ↓ albumin/creatinine ratio, compared to metoprolol (16%, *P*=0.003)

* At 5 months.GEMINI=Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives

Bakris GL, et al. *JAMA*. 2004;292:2227-2236.

Recommendation

- Beta-blockers in diabetes mellitus
  - Recommend the use of beta-blocker in type 2 diabetes patients with heart failure and/or history of myocardial infarction
  - Beta-blockers may be used safely for patients using blood pressure control
  - Glucose metabolism may be adversely affected by some beta-blockers

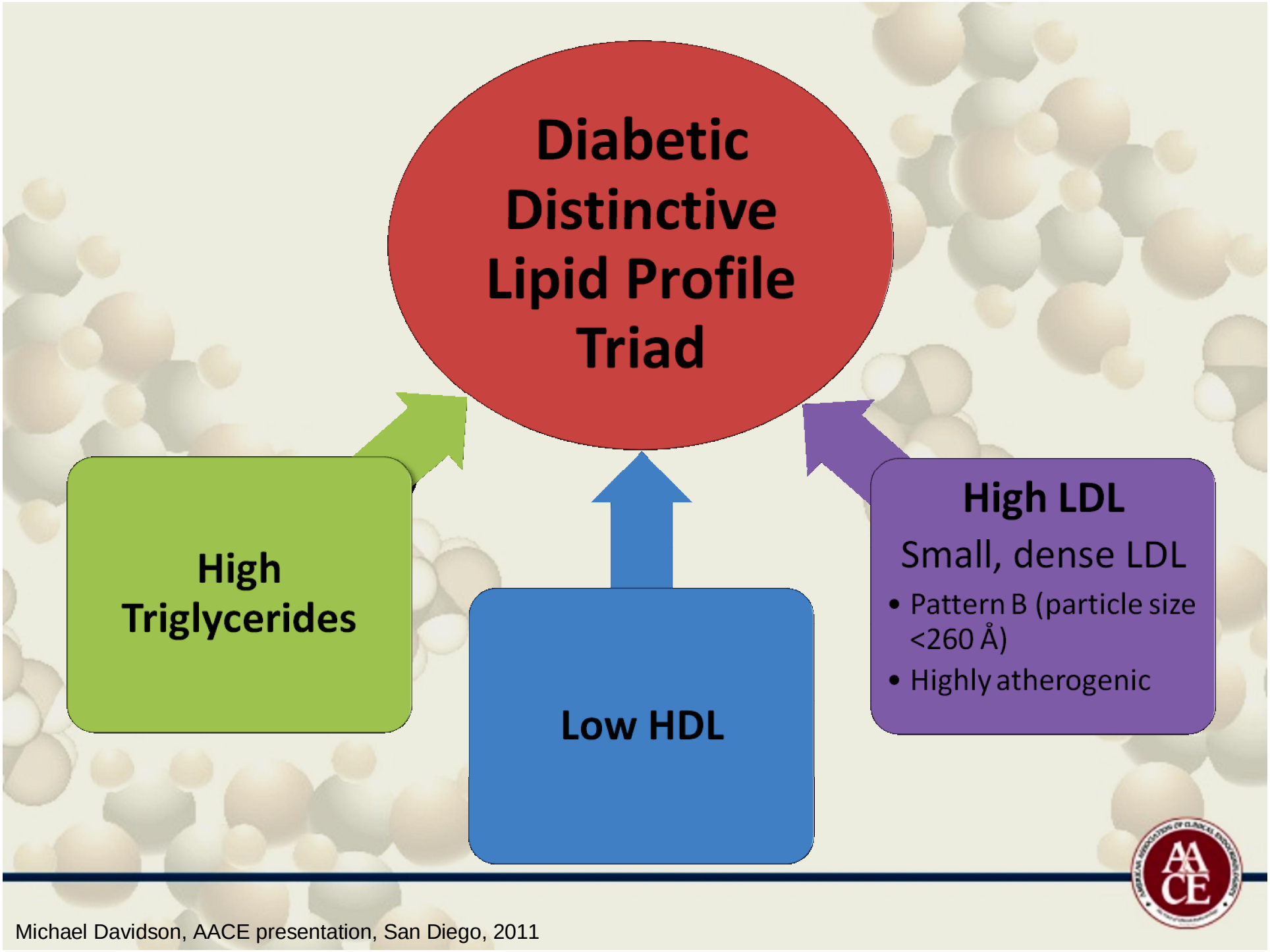
Compelling Indications for Individual Drug Classes

Compelling Indication	Recommended Drugs						Clinical Trial Basis
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT	
Heart failure	Å	Å	Å	Å		Å	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM
Post-myocardial infarction		Å	Å			Å	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS
High coronary disease risk	Å	Å	Å		Å		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE, EUROPA, INVEST
Diabetes	Å	Å	Å	Å	Å		NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			Å	Å			NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	Å		Å				PROGRESS

Aldo ANT = aldosterone antagonist

Chobanian AV et al. *Hypertension.* 2003;42:1206-1252.

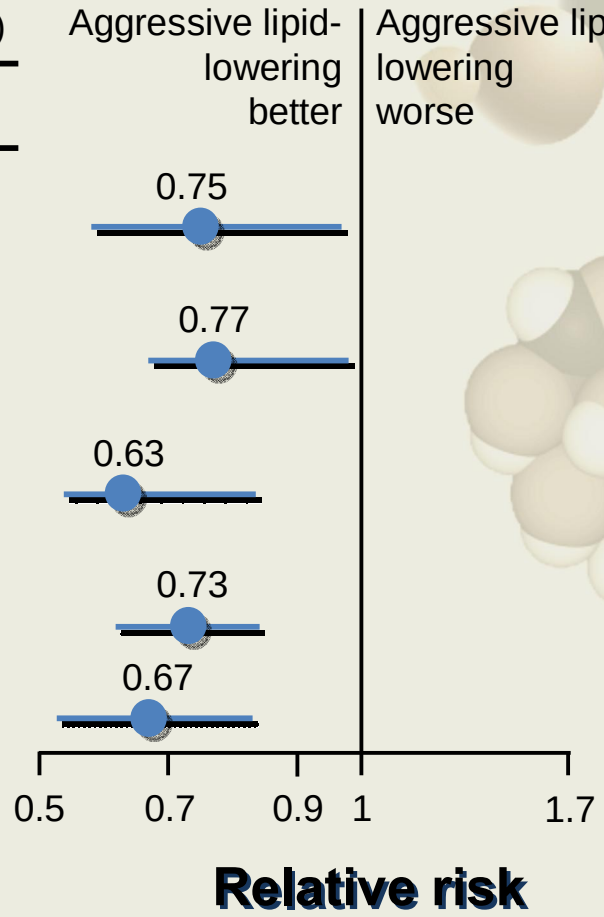
Lipids



Michael Davidson, AACE presentation, San Diego, 2011

Benefits of Aggressive LDL-C Lowering in Diabetes

	Primary event rate (%)		Aggressive lipid-lowering better	Aggressive lipid-lowering worse	P	Difference in LDL-C (mg/dL)
	Treatment	Control				
TNT						
Diabetes, CHD	13.8	17.9	0.75		0.026	22*
ASCOT-LLA						
Diabetes, HTN	9.2	11.9	0.77		0.036	35Å
CARDS						
Diabetes, no CVD	5.8	9.0	0.63		0.001	46Å
HPS						
All diabetes	9.4	12.6	0.73		<0.0001	39Å
Diabetes, no CVD	9.3	13.5	0.67		0.0003	39Å

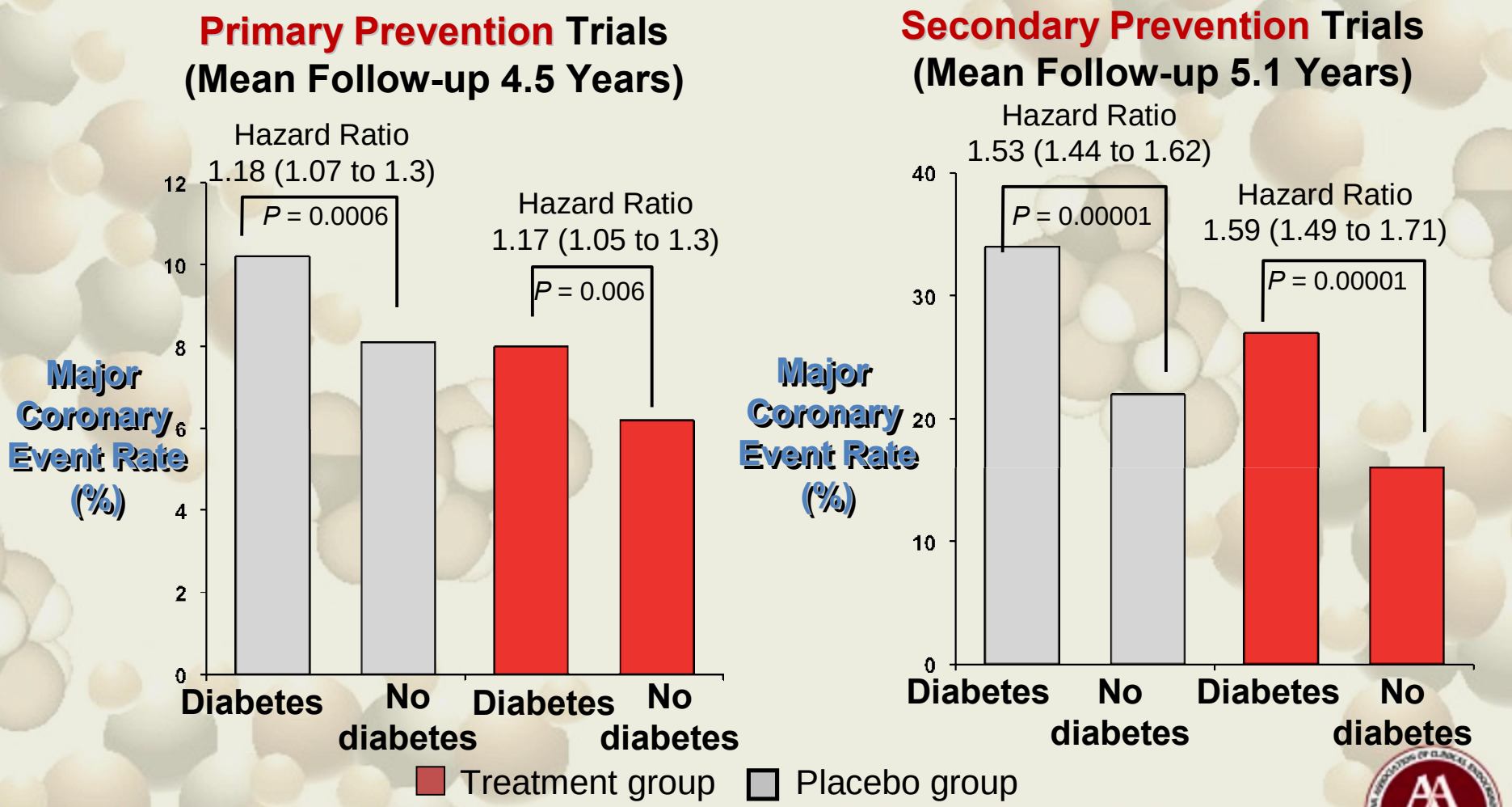


*Atorvastatin 10 vs 80 mg/day
ÅStatin vs placebo

Shepherd J et al. *Diabetes Care* 2006. Sever PS et al. *Diabetes Care* 2005. HPS Collaborative Group. *Lancet* 2003. Colhoun HM et al. *Lancet* 2004.

Efficacy of Lipid-lowering Drug Treatment for Patients With and Without Diabetes

(Meta-analysis of Randomized Controlled Trials)

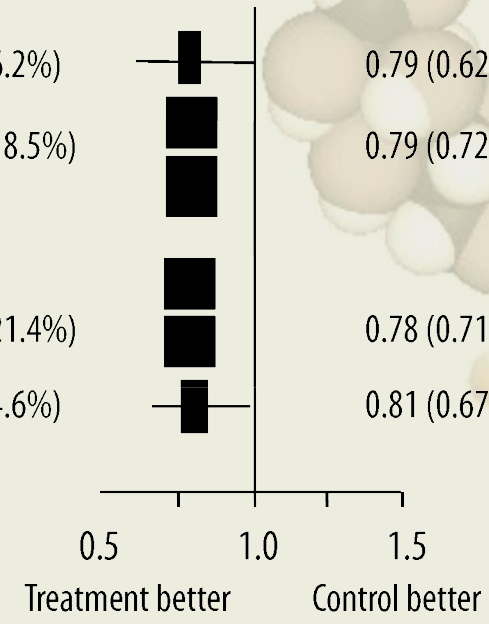


Costa J et al. *BMJ*. 2006;332:1115-1124.

Efficacy of Cholesterol-Lowering Therapy in 18,686 People with Diabetes in 14 Randomised Trials of Statins: A Meta-Analysis

Cholesterol Treatment Trialistsô(CTT) Collaborators

Groups	Events (%) Treatment	Control	RR(CI)	Test for heterogenity or trend
Type 1 diabetes	147 (20.5%)	196 (26.2%)	0.79 (0.62-1.01)	x^2_1=0.0;p=1.0
Type 2 diabetes	1318 (15.2%)	1586 (18.5%)	0.79 (0.72-0.87)	
Sex:				
Men	1082 (17.2%)	1332 (21.4%)	0.78 (0.71-0.86)	
Women	383 (12.4%)	450 (14.6%)	0.81 (0.67-0.97)	x^2_1=0.1;p=0.7



Global test for heterogeneity within subtotals: x^2_{13}=13.9;p=0.4

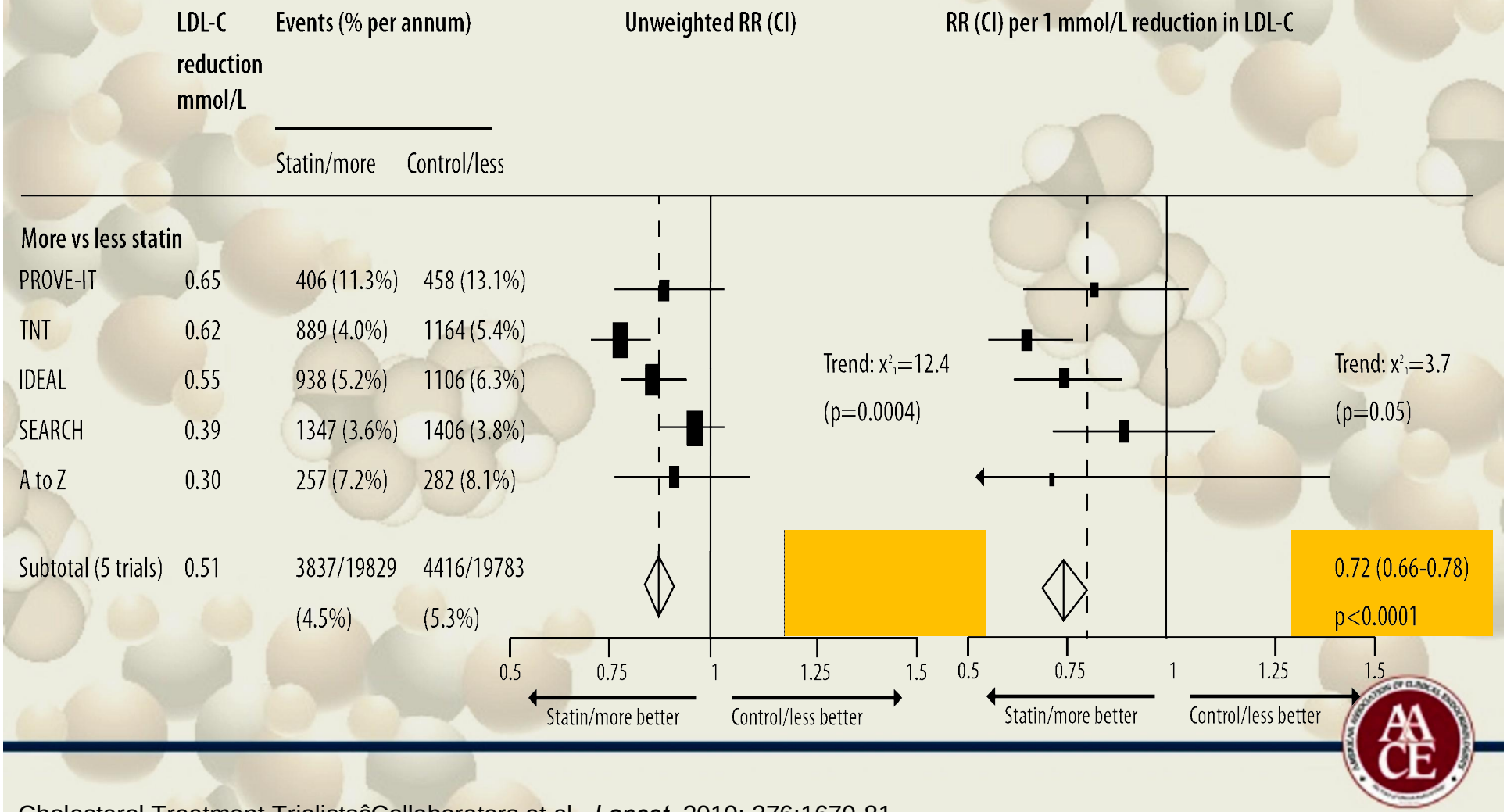
RR (99% CI)

RR (95% CI)

Cholesterol Treatment TrialistsôCollaborators et al. *Lancet*. 2008 Jan 12;371(9607):117-25.

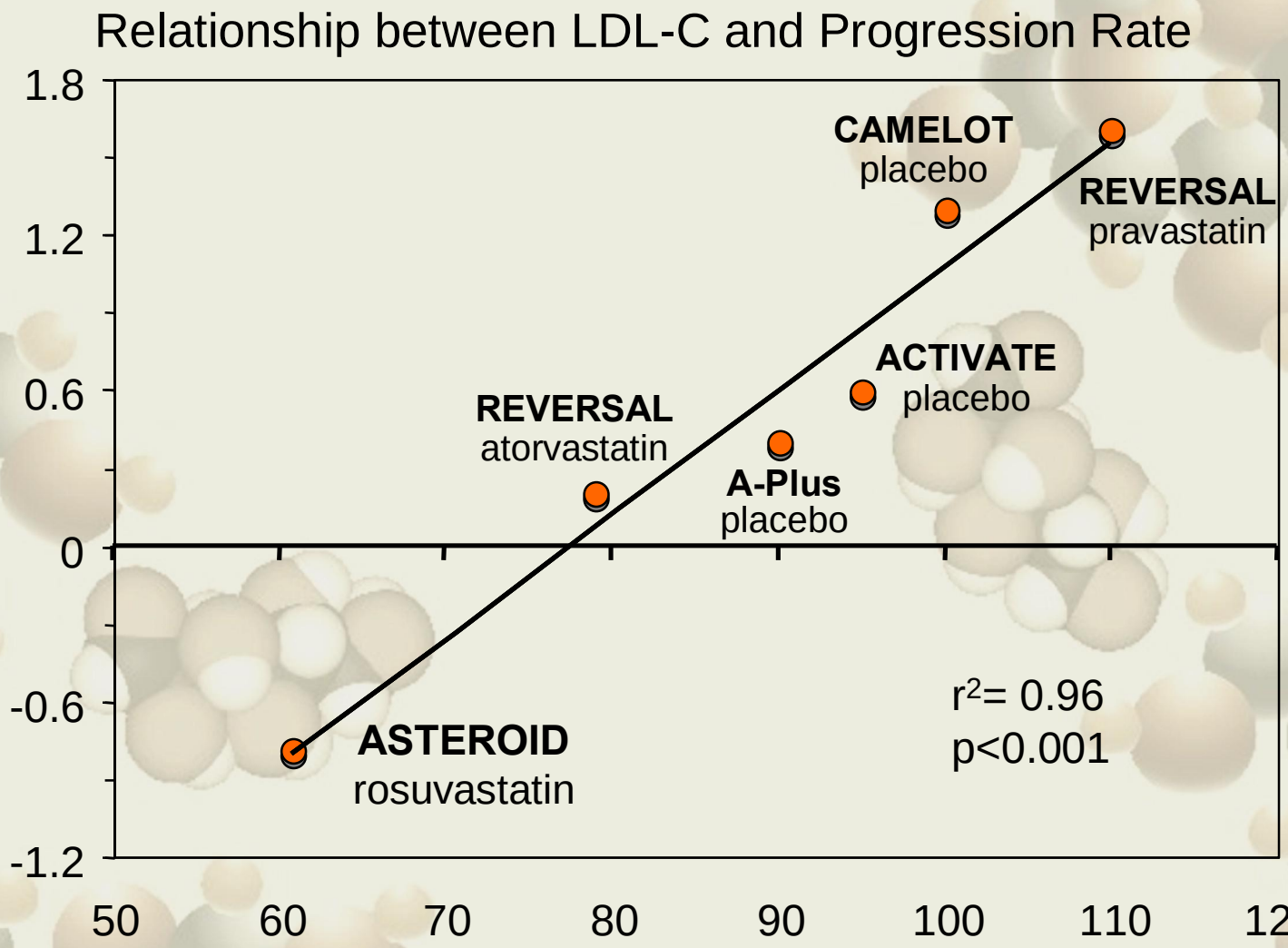
Efficacy and Safety of More Intensive Lowering of LDL Cholesterol: A Meta-Analysis of Data from 170,000 Participants in 26 Randomised Trials

Cholesterol Treatment Trialistsô(CTT) Collaborators



Cholesterol Treatment TrialistsôCollaborators et al. *Lancet*. 2010; 376:1670-81.

Recent Coronary IVUS Progression Trials



Hartmann M et al. *Eur J Echocardiogr*. 2011. 12(4):313-321

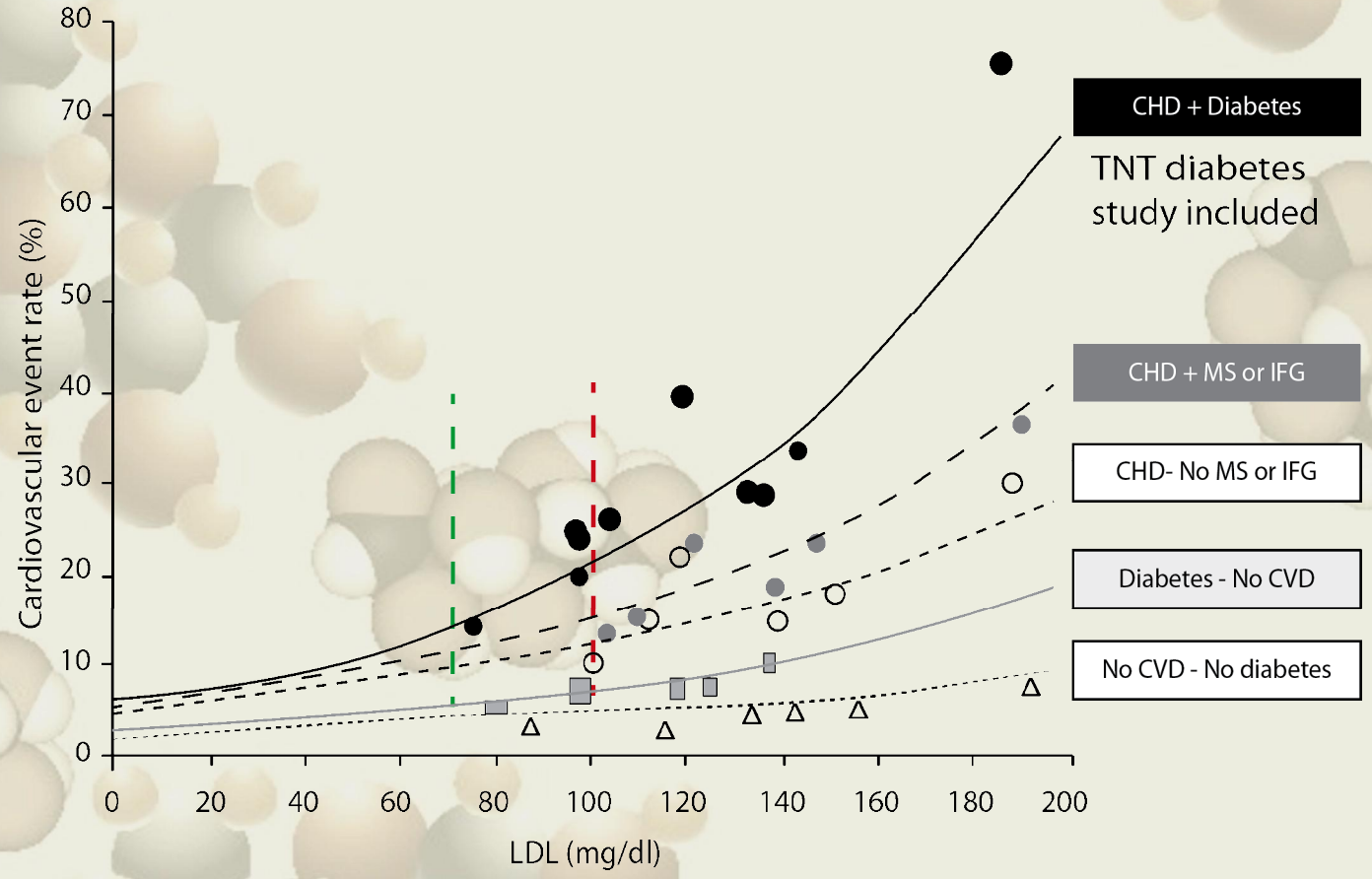
Statins – Conclusions

- Statins are at least as beneficial, if not more so, in reducing CVD risk as aspirin
- If a million at-risk patients with high cholesterol were treated with a statin:
- About 10,000 heart attacks or strokes could be prevented each year
  - 1-2 patients might experience a serious side effect
  - The problem is not that too many patients are having adverse effects with statins ï the problem is that too many people may be avoiding statins because of an unnecessary fear of adverse effects

Don't fear side effects from statins…
fear heart disease

When To Treat

Treat Patients With the Greatest Absolute Risk the Most Aggressively Risk Curve Concept



This figure shows the intent-to-treat LDL cholesterol level and risk for hard cardiovascular events (nonfatal myocardial infarction, CHD death, and stroke) by the presence of CHD, metabolic syndrome, impaired fasting glucose, or diabetes in placebo-controlled statin trials of approximately 5 years in duration.

Robinson JG et al. *Am J Cardiol* 2006 Nov 15. 98(10):1405-8.

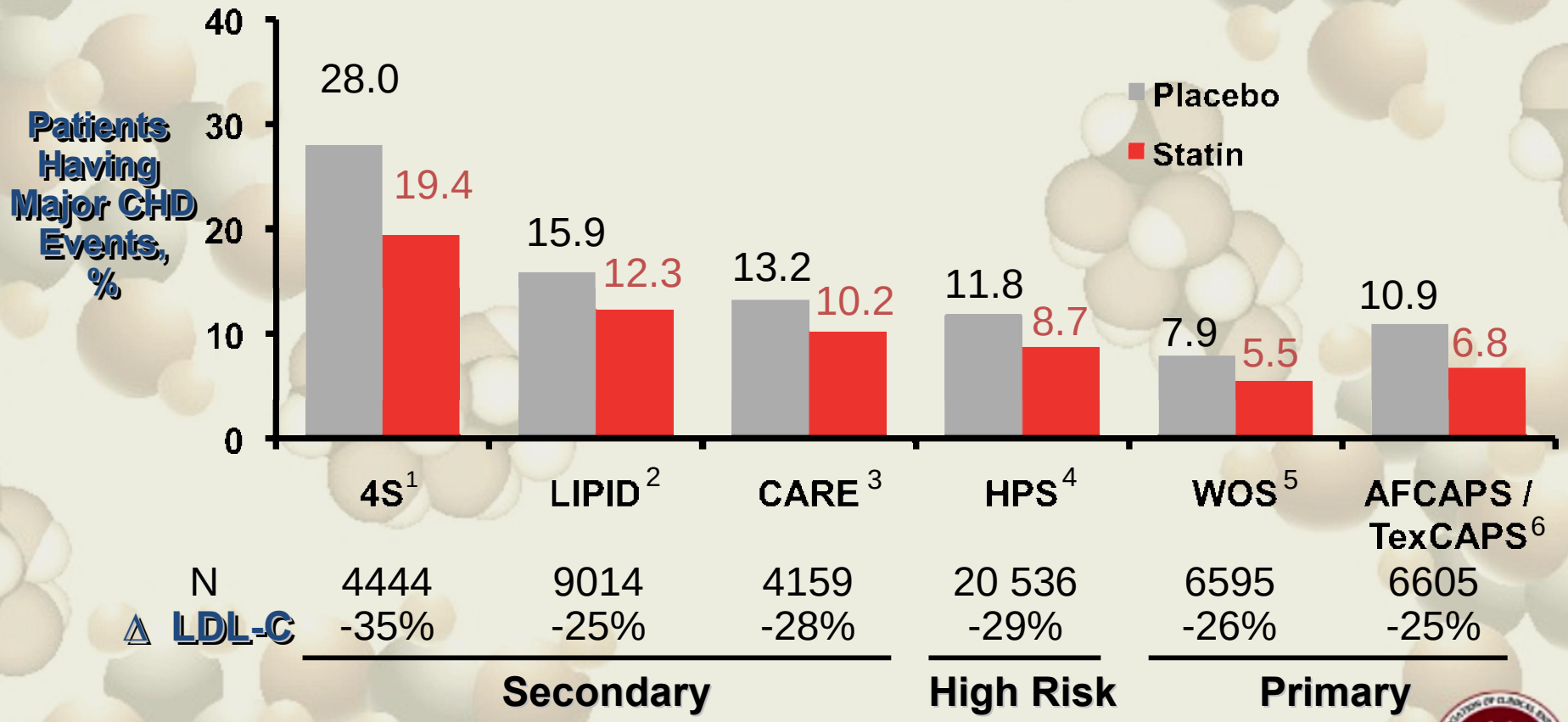
Residual Cardiovascular Risk, Even After Treatment With Statins

- Despite high-dose statin therapy, there is a high residual risk in patients with diabetes, low HDL, elevated triglycerides, and other risk factors
- Therefore, these other risk factors should be addressed

Michael Davidson, AACE 2011, presentation

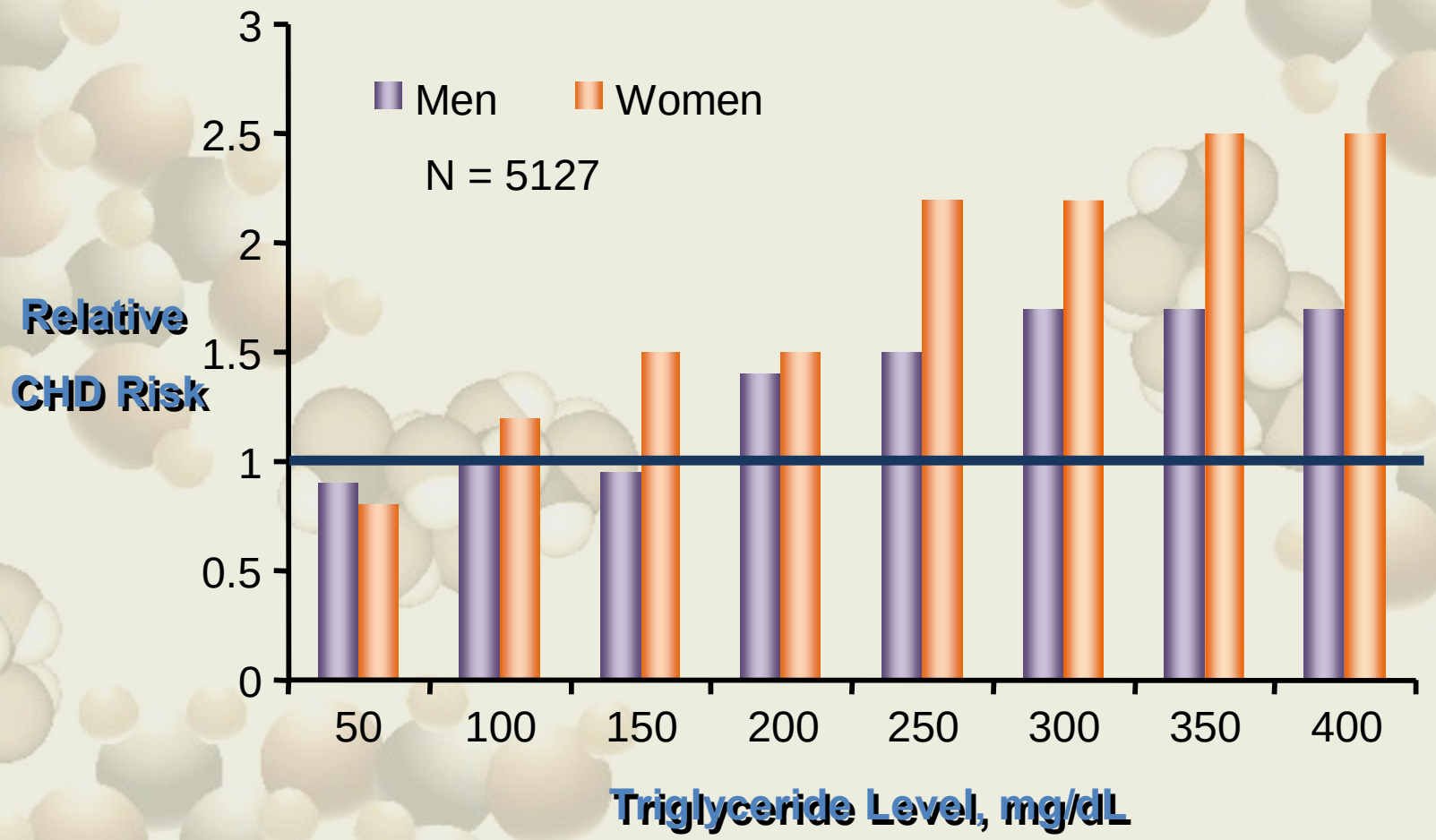
Residual Cardiovascular Risk in Major Statin Trials

CHD events still occur in patients treated with statins



[1] 4S Group. *Lancet.* 1994;344:1383-1389.
[2] LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[3] Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
[4] HPS Collaborative Group. *Lancet.* 2002;360:7-22.
[5] Shepherd J, et al. *N Engl J Med.* 1995;333:1301-1307.
[6] Downs JR, et al. *JAMA.* 1998;279:1615-1622

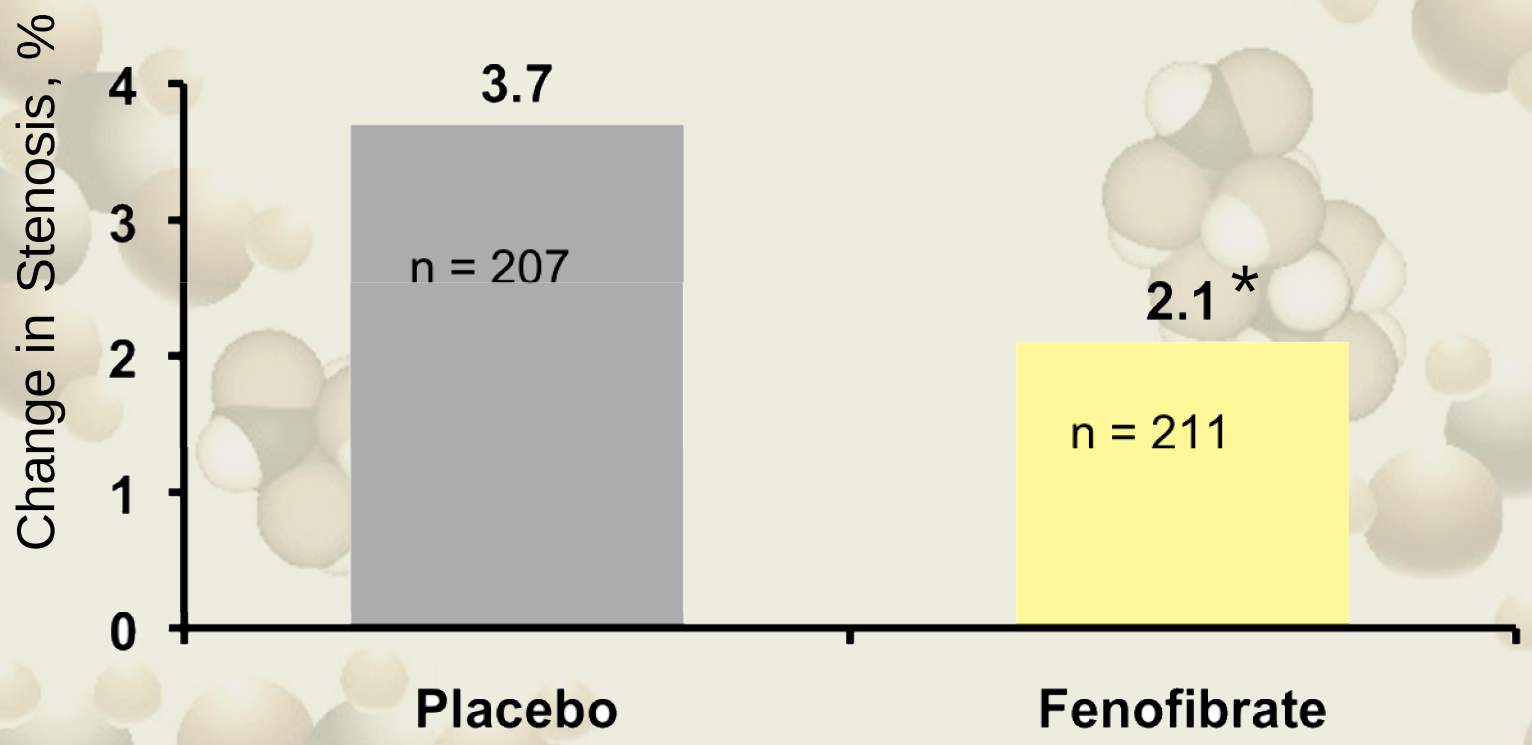
Risk of CHD by Triglyceride Level
The Framingham Heart Study



Castelli WP. *Am J Cardiol.* 1992;70:3H-9H.

DAIS: Effect of Fenofibrate on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

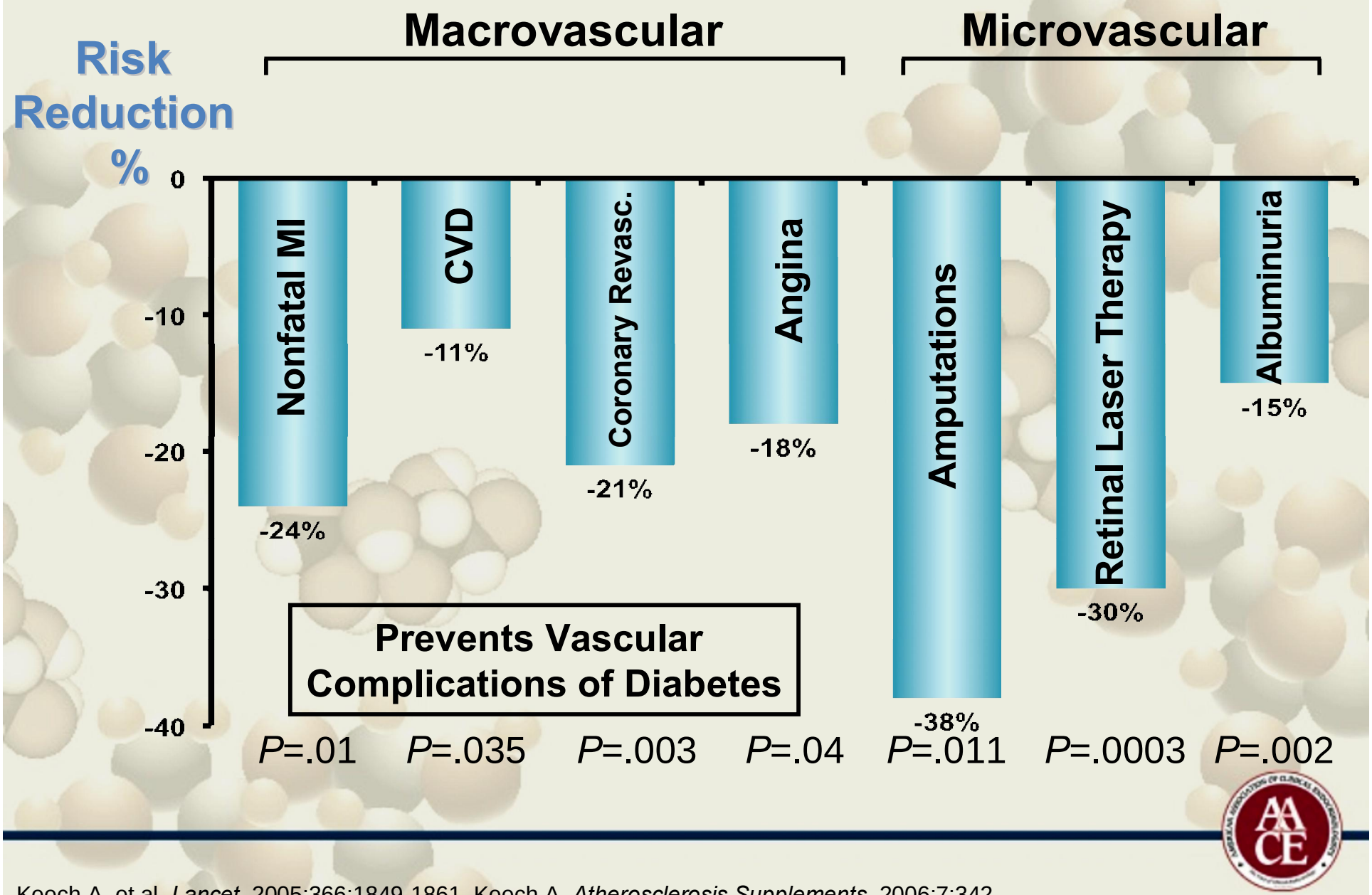
Quantitative Coronary Angiography



*P=.02 vs placebo

Diabetes Atherosclerosis Intervention Study. *Lancet.* 2001;357:905-910.

FIELD: Clinical Benefits of Fenofibrate



Keech A, et al. *Lancet.* 2005;366:1849-1861. Keech A. *Atherosclerosis Supplements.* 2006;7:342.

HDL-C Is a Modifier of Risk at All Levels of LDL-C

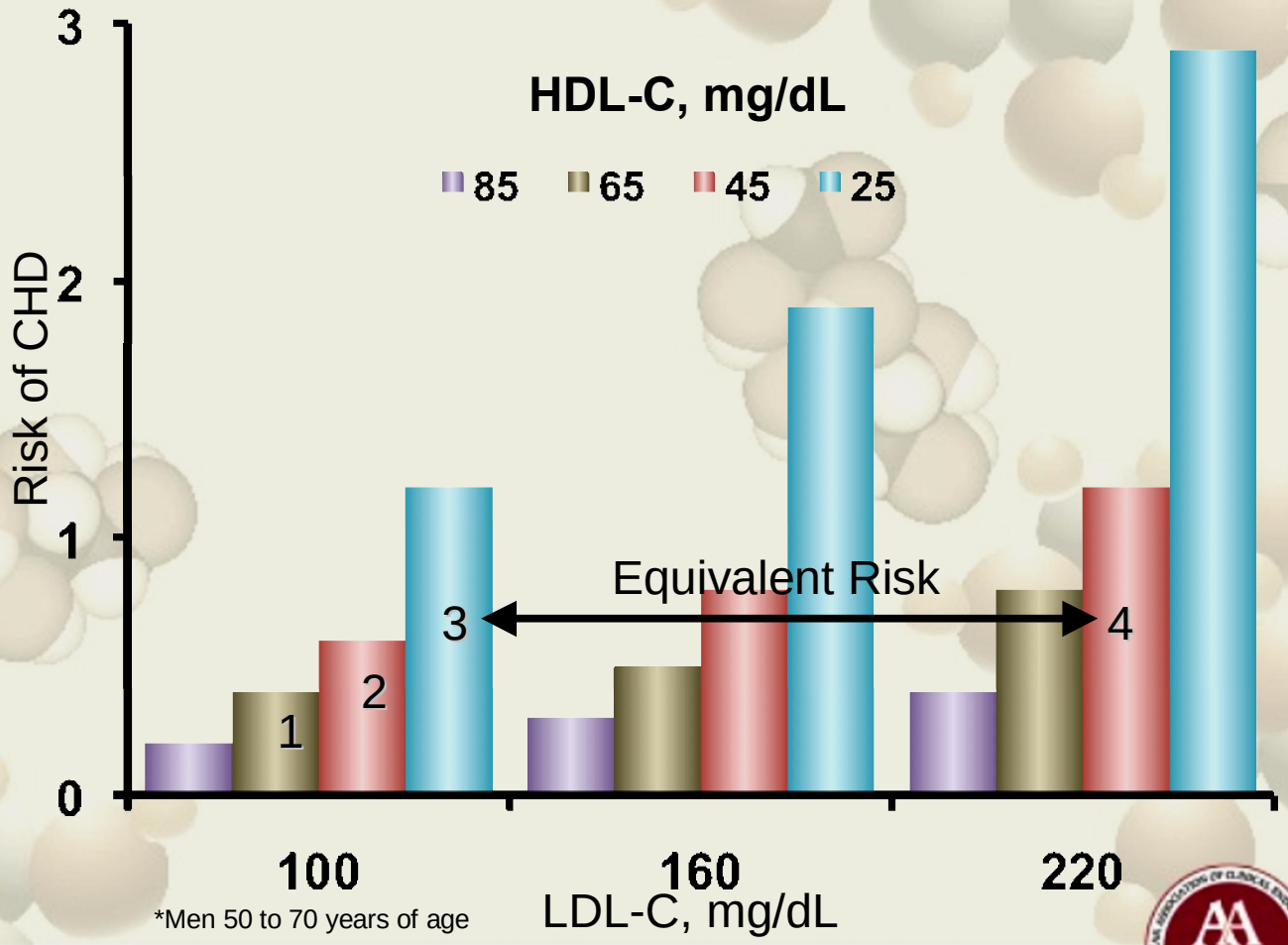
The Framingham Study*

Patient 1
LDL-C 100 mg/dL
HDL-C 65 mg/dL
Risk level 0.4

Patient 2
LDL-C 100 mg/dL
HDL-C 45 mg/dL
Risk level 0.6

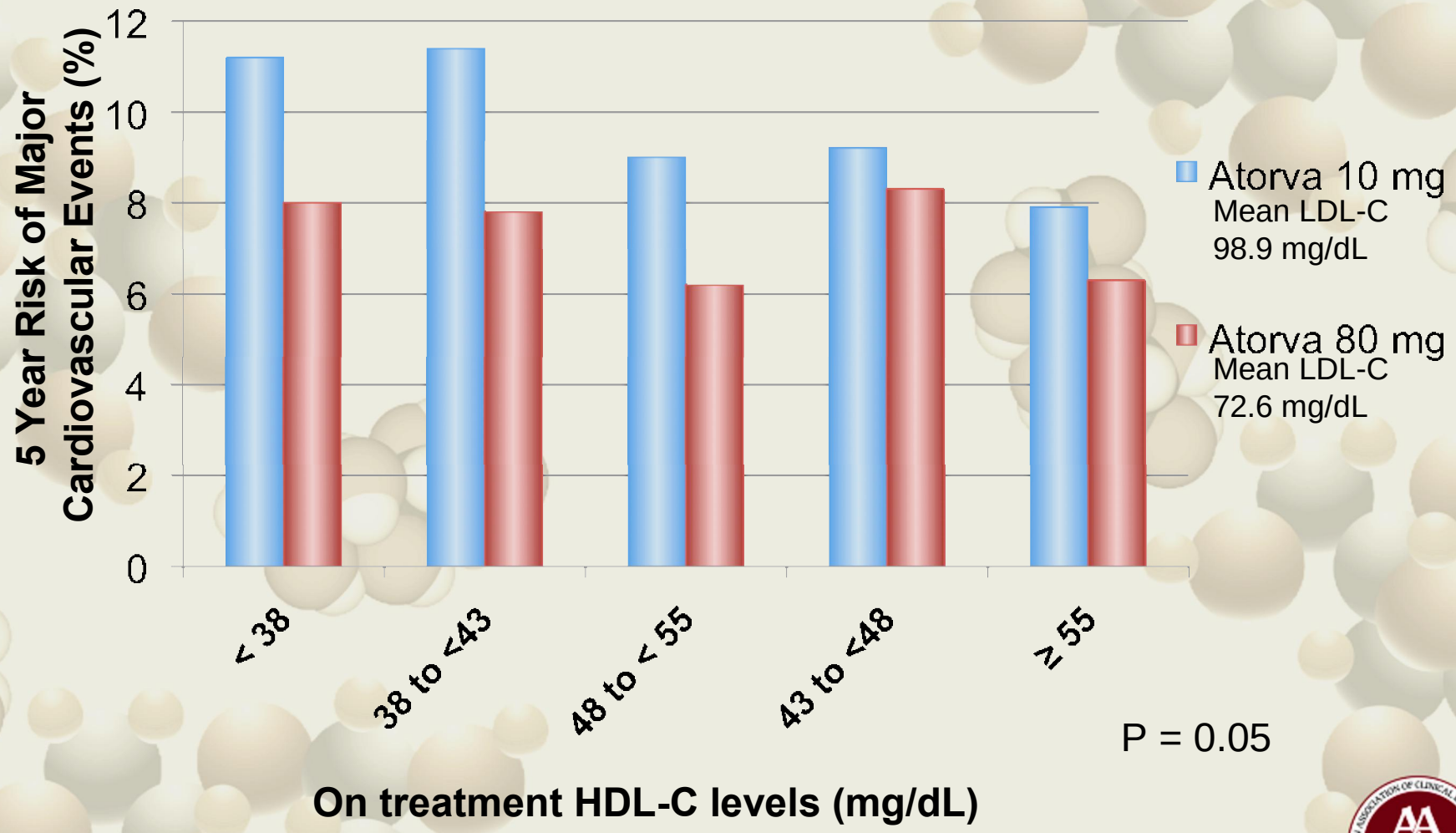
Patient 3
LDL-C 100 mg/dL
HDL-C 25 mg/dL
Risk level 1.2

Patient 4
LDL-C 220 mg/dL
HDL-C 45 mg/dL
Risk level 1.2



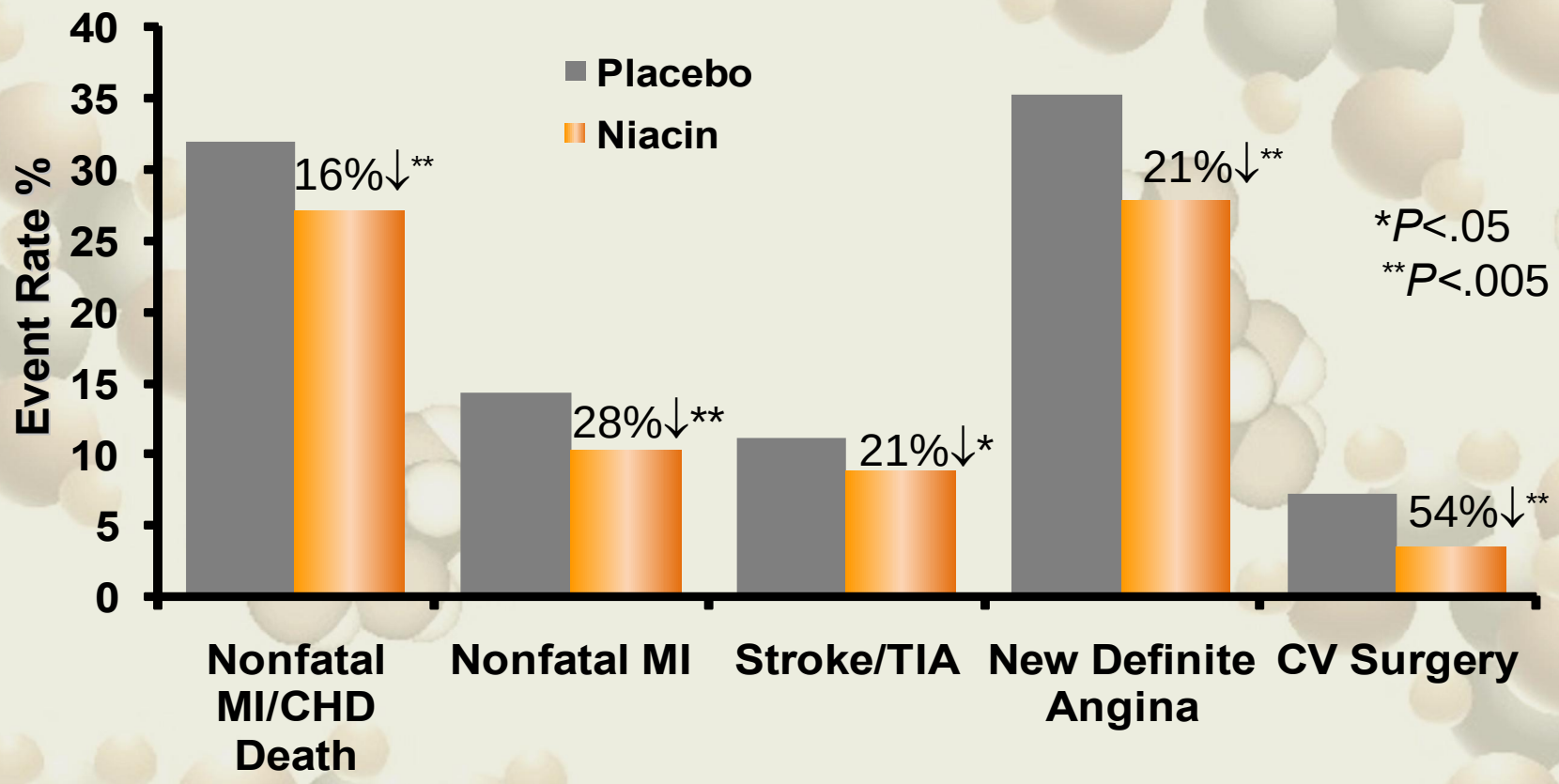
Castelli WP. *Can J Cardiol*. 1988;4(suppl A):5A-10A.

Cardiovascular Events in TNT According to On-treatment HDL-C



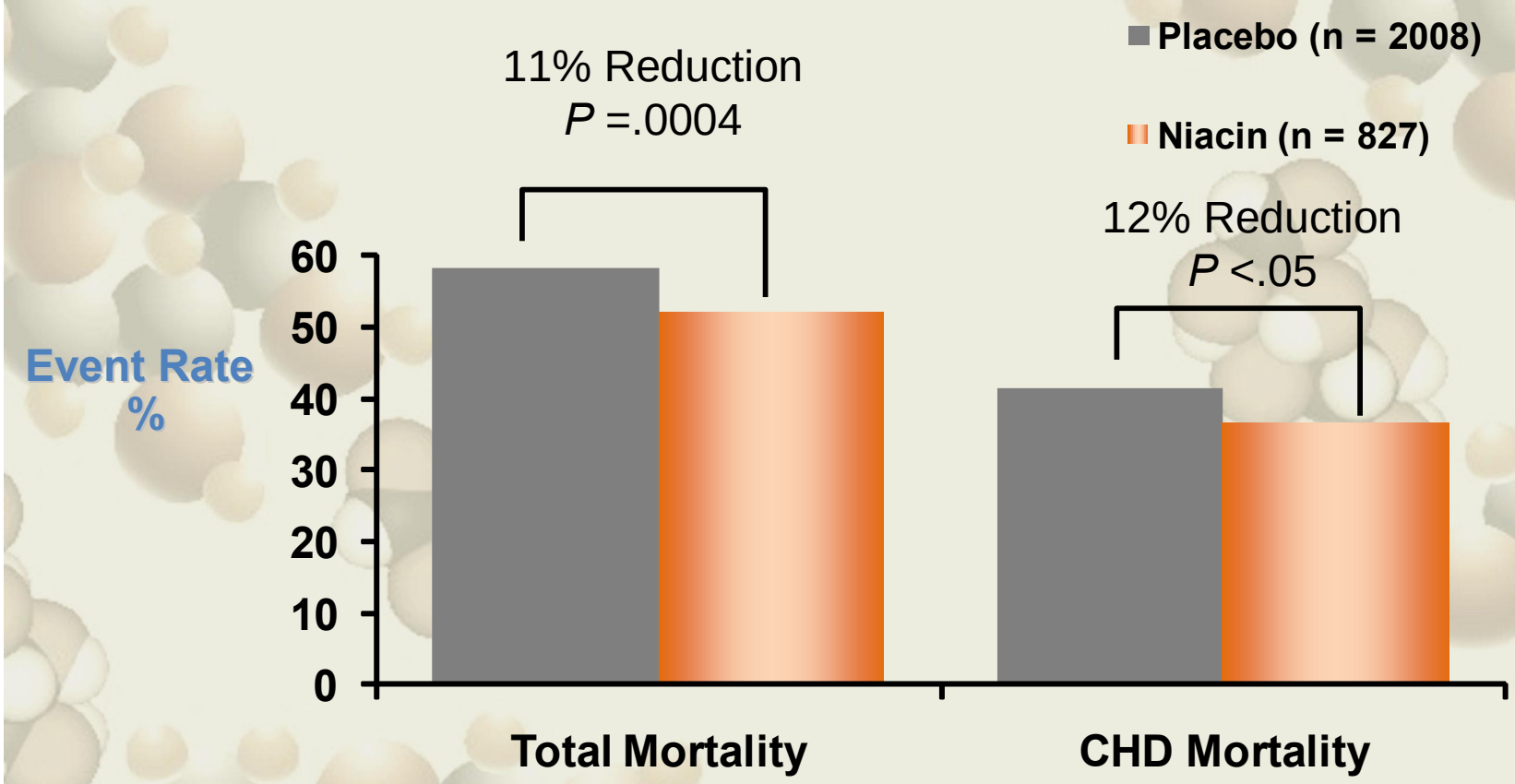
Barter et al. *N Engl J Med*. 2007; 357:1301-1310.

Coronary Drug Project (CDP)
Complete Treatment Follow-up (Mean 6.2 Years)



Brown BG, et al. Nicotinic Acid, In: Ballantyne CM (Ed) *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. In Press.

CDP: 15-Year Follow-Up



Canner PL, et al. *J Am Coll Cardiol.* 1986;8:1245-1255. Canner PL, et al. *J Am Coll Cardiol.* 2005;95:254-257.

Program Summary

- Patients with diabetes and the metabolic syndrome have **atherogenic dyslipidemia** and an increased risk for CVD
- Although statin therapy is effective in lowering LDL-C, **residual CVD risk remains** after statin therapy
- Clinical trial evidence indicates that **fibrate** therapy is beneficial in reducing CVD risk, particularly in patients with diabetes and the metabolic syndrome; fenofibrate/statin combination therapy is well tolerated and safe

Kumar A, et al. *Vasc. Health and Risk Mgmt.* 2010;6:665-669.

Program Summary cont.

- Clinical trial data support the efficacy of **niacin** in reducing CVD risk when used alone and in combination with statins or other LDL-lowering agents
- Niacin has been in clinical use for 4 decades, with an established safety profile, including use in combination therapy with statins
  - Niacin ER/lovastatin is U.S. FDA-approved
- To reduce residual CVD risk, lipid **abnormalities beyond LDL-C** (non-HDL-C, TG, HDL-C) should be intensively treated

So, plan…

Cardiovascular Screening

- Macrovascular Screening
- A graded exercise test (GXT)* recommended for those planning moderate to high intensity IFé
  - >35 years of age
  - Type 2 diabetes >10 years duration
  - Type 1 diabetes >15 years duration
  - Presence of other CVD risk factors
  - Presence of Microvascular disease
  - Peripheral vascular disease (PVD)
  - Autonomic neuropathy

*Stress or Treadmill test to determine a heart condition

Antiplatelet Agents in Diabetes: 2011

- Primary prevention (75-162 mg/day):
  - Type 1 or type 2 diabetes at increased CV risk (10 yr risk > 10%)
  - Men >50 yr or women >60 yr with 1+ additional major risk factor
    - Family history of CVD, HTN, smoking, dyslipidemia, or albuminuria
  - Not sufficient evidence to recommend asprin for pirmary prevention in lower risk individuals
- Secondary prevention (75-162 mg/day):
  - Use aspirin therapy as a secondary prevention strategy in those with diabetes with a history of CVD

American Diabetes Association. *Diabetes Care.* 2011;34(1):S11-61

ABCs of CVD Risk Management

	Intervention	Goals
A	➢ Anti-platelets/anticoagulants ➢ ACE inhibitors/ARBs ➢ Anti-anginals	➢ Treat all high-risk patients with one of these ➢ Optimize BP especially if CVD, type 2 diabetes, or low EF present ➢ Relieve anginal symptoms, allow patient to exercise
B	➢ BP control ➢ β-blockers	➢ Aim for BP <130/85 mm Hg, or <130/80 mm Hg for type 2 diabetes ➢ Post MI or low EF

CVD=cardiovascular disease; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; BP=blood pressure; EF=ejection fraction; MI=myocardial infarction.

Braunstein JB et al. *Cardiol Rev*. 2001;9:96-105.

ABCs of CVD Risk Management

	Intervention	Goals
C	➢ Cholesterol management	➢ LDL-C targets, ATP III guidelines • CHD, CHD risk equivalents: <100 mg/dL • ≥2 RF: <130 mg/dL • 0-1 RF: <160 mg/dL ➢ HDL-C: ≥40 mg/dL (men) ≥50 mg/dL (women) ➢ TG: <150 mg/dL
	➢ Cigarette-smoking cessation	➢ Long-term smoking cessation

LDL-C = Low Density Lipoprotein-C; ATP =Adenosine Triphosphate; CHD = Coronary Heart Disease; HDL-C = High Density Lipoprotein-C; TG = Triglycerides

Braunstein JB et al. *Cardiol Rev*. 2001;9:96-105. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

ABCs of CVD Risk Management

	Intervention	Goals
D	➢ Dietary/weight counseling ➢ Diabetes management	➢ Achieve optimal BMI ➢ ↓ saturated fats; ↑ fruits, vegetables, fiber ➢ Achieve A1C <7%
E	➢ Exercise ➢ Education of patients and families	➢ Improve physical fitness (aim for 30 min/d on most days per week) ➢ Optimize awareness of CAD risk factors

BMI=body mass index; A1C=glycosylated hemoglobin; CAD=coronary artery disease.

Braunstein JB et al. *Cardiol Rev*. 2001;9:96-105.

Treating the ABCs Reduces Diabetic Complications

Strategy	Complication	Reduction of Complication
Blood glucose control	ĭ Myocardial infarction	↓ **37%**[1]
Blood pressure control	ĭ Cardiovascular disease	↓ **51%**[2]
	ĭ Heart failure	↓ **56%**[3]
	ĭ Stroke	↓ **44%**[3]
	ĭ Diabetes-related deaths	↓ **32%**[3]
Lipid control	ĭ Coronary heart disease mortality	↓**35%**[4]
	ĭ Major coronary heart disease event	↓**55%**[5]
	ĭ Any atherosclerotic event	↓**37%**[5]
	ĭ Cerebrovascular disease event	↓**53%**[4]

[1] UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.
[2] Hansson L, et al. *Lancet*. 1998;351:1755-1762.
[3] UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.
[4] Grover SA, et al. *Circulation*. 2000;102:722-727.
[5] Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.